Maternity Outcomes and Access following Regulatory Changes for Isotretinoin Prescribing in New Zealand

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MASTERS' RESEARCH THESIS

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List of Abbreviations

BPAC	Best Practice Advocacy Centre
DHB	District Health Board
DLQI	Dermatology Life Quality Index
EU	European Union
FDA	United States Food and Drug Administration
GP	general practitioner
HDL	high-density lipoprotein
ICD-10-AM	International Statistical Classification of Diseases and Related Health problems, 10th Revision, Australian Modification
IBD	Inflammatory Bowel Disease
NHI	National Health Index
NMDS	National Minimum Dataset
MELAA	Middle Eastern/Latin American/African
PHARMAC	Pharmaceutical Management Agency
PHO	Primary Health Organisation
PPP	Pregnancy Prevention Programme
REMS	Risk Evaluation and Mitigation Strategy
SMART	System to Manage Accutane-Related Teratogenicity
SQL	Structured Query Language
TOP	Termination of Pregnancy
UK	United Kingdom
US	United States

Glossary of Agencies

Best Practice Advocacy Centre ……BPAC

United States Food and Drug Administration…….FDA

Pharmaceutical Management Agency ……PHARMAC

Acknowledgements

I am extremely grateful to my two supervisors Professor Susan Dovey and Dr Alesha Smith who have always shown enthusiasm for my research and supported me throughout this journey. I have been very fortunate to have your patience and complementary skill sets to oversee my work. I wish to also thank Professor Murray Tilyard, Dr Hywel Lloyd and the staff at BPAC CS for their support of this research. I am most thankful to my husband and children, Ray, Charlotte, Caroline and Henry, who have allowed me the time to complete my postgraduate studies and this project. I hope I have inspired in you a desire to search for the important answers and to make a difference.

Conflict of Interest Statement

Jenny McElroy is an employee of BPAC CS LP who are the providers of the Isotretinoin Decision Support tool in this study.

Abstract

Aims: Oral isotretinoin is an effective treatment for severe acne that is teratogenic. On 1 March 2009 funded access to oral isotretinoin in New Zealand was extended from dermatologist-only to also include prescriptions written by other prescribers where a dermatologist, vocationally registered general practitioner (GP) or nurse practitioner had obtained a Special Authority for this patient and medication. At the time of the change the Pharmaceutical Management Agency (PHARMAC) funded the development of an electronic decision support tool for primary care to support the safe prescribing and use of isotretinoin. Regular review of health outcomes was recommended to ensure the widening of funded access did not have negative effects on the health of the population.

This study aimed to examine the previously identified inequitable isotretinoin access to determine if the change in funded prescriber influenced isotretinoin dispensing by ethnicity, age, gender, or deprivation level. The study also investigated terminations of pregnancy (TOPs) and potentially exposed live births following isotretinoin dispensing in women with different prescriber-types and compared these rates in women for whom the prescriber used the Best Practice Advocacy Centre (BPAC) isotretinoin decision support tool to support their prescribing with the rates in women whose prescriber did not.

Methods: Retrospective prescription data for the 8 years from 1 March 2007 to 1 March 2015 were analysed to determine how access to isotretinoin changed in the twelve month periods before and after the funding change. Using National Health Index (NHI) codes, maternity outcomes for women who had isotretinoin dispensed during the study period were analysed with regard to TOP and exposed live births. The rates of these adverse maternity outcomes were then compared for different prescriber-types and for women whose clinician used the BPAC decision support tool to guide their prescribing.

Results: The use of isotretinoin has continued to increase since the change in funding and people living in more deprived areas (as defined by the NZDep Index), and Maori, Pacific and Asian people have had a proportionally larger increase in numbers accessing isotretinoin. General practitioners (GPs) now prescribe more isotretinoin than dermatologists.

The TOP and exposed live birth rate following isotretinoin prescription is similar in women prescribed the drug by dermatologists and GPs. These clinicians prescribe the majority of isotretinoin in New Zealand and the rate of TOP within six months of an isotretinoin prescription is around 16-23% of that for all females aged 15-44 in New Zealand. However the female patients of other clinicians who prescribe isotretinoin much less frequently than dermatologists or GPs have TOPs within six months of isotretinoin at higher rates. Up to 16 live births per year in New Zealand are potentially exposed to isotretinoin with dermatologists, GPs and other clinicians all prescribing for the women involved. Use of the BPAC decision support tool to guide the prescribing of isotretinoin resulted in a lower rate of TOP and exposed births than occurred in patients where it was not used.

Conclusions: Isotretinoin is proportionally more accessible to Asian, Maori and Pacific people and people in lower socio-economic groups than it was when funded only through dermatologists. However Europeans and the least deprived groups continue to be the people who use isotretinoin in the greatest numbers.

GPs are now the largest group of isotretinoin prescribers in New Zealand but this has not resulted in higher rates of TOP or potentially exposed pregnancies than when prescribing was funded only through dermatologists. However female patients of other prescribers, who do not prescribe isotretinoin as frequently, have higher rates of TOP following isotretinoin dispensing and more potentially exposed live births.

The BPAC Decision Support tool helped achieve better maternity outcomes for women accessing isotretinoin where it was used to guide prescribing. The challenge for health managers is to address barriers to its use, to invest in supporting all isotretinoin prescribers to use decision support, and to involve female patients in adhering to contraceptive guidelines.

1 Introduction

Oral isotretinoin is an effective treatment for severe acne that is known to be teratogenic and to cause an increased risk of spontaneous abortion when used during pregnancy. On 1 March 2009 funded access to oral isotretinoin in New Zealand was extended from dermatologist-only to also include prescriptions written by other prescribers where a dermatologist, vocationally registered general practitioner (GP) or nurse practitioner had obtained a Special Authority for this patient and medication. At the time of the change the Pharmaceutical Management Agency (PHARMAC) funded the development of an electronic decision support tool for primary care to support the safe prescribing and use of isotretinoin.

Prior to this change in funding, a clear linear association between the use of isotretinoin and deprivation level has been shown in New Zealand with people living in the least deprived areas (as defined by NZDep Index) shown to be two and a half times as likely to access isotretinoin compared with people from the most deprived quintile[1]. Maori and Pacific people were also far less likely to access isotretinoin than those of other ethnicity (mainly NZ European)[1].

This study aimed to examine this previously identified inequitable isotretinoin access to determine if the change in funded prescriber influenced isotretinoin dispensing by ethnicity, age, gender, or deprivation level. The study also investigated terminations of pregnancy (TOPs) within six months of an isotretinoin prescription and potentially exposed live births with different prescriber-types and compared TOP rates in women for whom the prescriber used the Best Practice Advocacy Centre (BPAC) isotretinoin decision support tool to support their prescribing with TOP rates in women whose prescriber did not.

The research questions for the study were:

1) Has the use of funded isotretinoin in New Zealand from 1 March 2007 to 1 March 2015 changed with regard to age, gender, ethnicity, and deprivation level?

2) Has widened access to funded isotretinoin correlated to a change in the rate of TOP following isotretinoin dispensing and the number of potentially isotretinoin-exposed live births in New Zealand?

3) Is there a difference in the TOP or exposed live birth rate between different isotretinoin-prescriber types in New Zealand from 1 March 2007 to 1 March 2015?

4) Is there a difference in the TOP or exposed live birth rate between women whose isotretinoin prescriber accessed the BPAC decision support tool for them and women whose prescriber did not?

This study is important because review of the adverse maternity outcomes and access to isotretinoin has not been conducted since this funding change in order to evaluate the impacts on the health of New Zealanders.

2 Background

This chapter describes the condition of acne, its treatment and the use of oral isotretinoin in the treatment of severe acne including the risks associated with its use.

2.1 Acne

Vulgaris is the medical term for common[2] and acne vulgaris is the common type of acne prevalent in 99% of acne cases.[3]

2.1.1 Pathogenesis of acne

Acne vulgaris is caused by the obstruction and inflammation of sebaceous follicles, which are a subtype of the pilosebaceous units of the skin. Sebaceous follicles consist of a sebaceous gland and a rudimentary hair growing out of the follicle. Figure 1 illustrates the position of the sebaceous gland and hair follicle in the dermis layer of the skin.

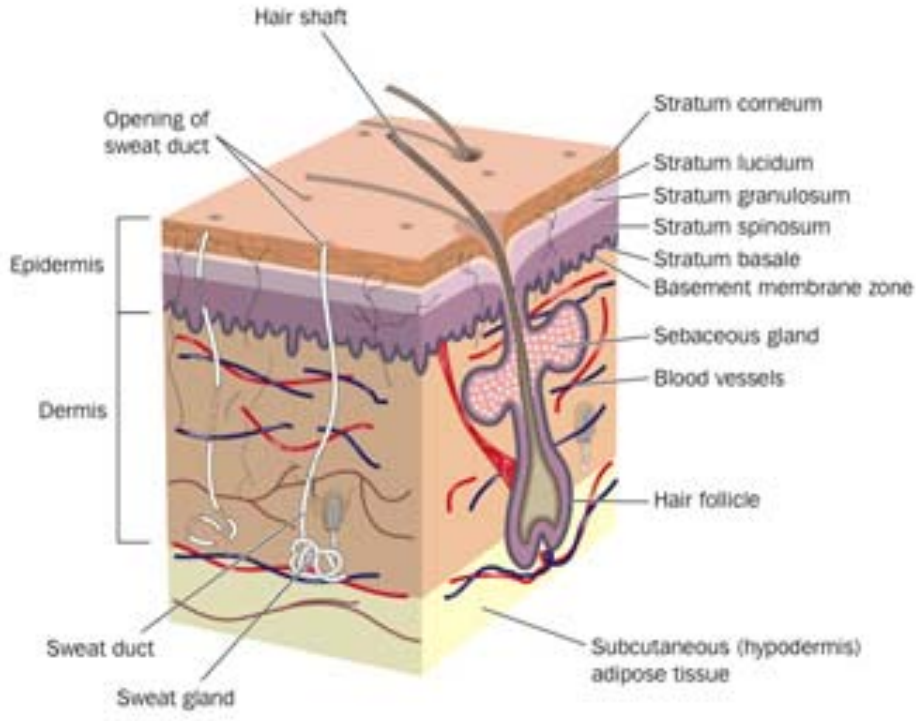


Figure 1: Structure of the Skin[4]

Source: [Internet] 2014 [cited 2016 Apr 6]. http://www.clinimed.co.uk/Wound-Care/Education/Wound-Essentials/Structure-and-Function-of-the-Skin.aspx

The primary lesion of acne is a microcomedo, a microscopic lesion invisible to the eye. Some microcomedones evolve into either non-inflammatory comedo (open or closed), or inflammatory lesions such as papules, pustules, nodules (firm lumps) or cysts (fluid-filled cavities).

The formation of a microcomedo involves a complex interplay of four pathogenic factors:

- altered follicular growth and differentiation (keratinisation),
- hyperplasia of sebaceous glands with seborrhoea,
- over-colonisation of sebaceous follicles with *Propionibacterium acnes.*
- the host immune response and inflammation.[5]

Propionibacterium acnes is a harmless member of the resident flora of the skin which proliferates in the environment of the microcomedo and is present in increased numbers

in people who have acne. The bacteria produce enzymes that hydrolyse sebum into free fatty acids and these stimulate inflammatory processes in the skin. As the wall of the follicle becomes inflamed, a reddened pimple appears on the skin surface. With increased sebum production, obstruction and colonisation of bacteria, the follicle ruptures and spills its contents into the dermis where the inflow of neutrophils causes the formation of pustules. If severe inflammation is present, this can lead to the formation of nodules and subsequent cysts.[6]

2.1.2 Types of Acne

The most common variants of acne are comedonal acne, papulopustular acne and nodular/conglobate acne. Comedonal acne involves non-inflamed lesions which are seen as blackheads, where comedones are open, and as whiteheads where they are closed. Clinically non-inflamed lesions develop from the subclinical microcomedo and closed comedones will often be inconspicuous with no visible follicular opening.[7]

Papulopustular acne involves inflammatory lesions which may be either superficial (less than 5 mm in diameter) or, in more severe disease, deeper pustules or nodules. Inflammatory macules represent regressing lesions that may persist for many weeks and contribute significantly to the general inflammatory appearance of the acne.[7]

Nodular acne involves nodules which are firm inflamed lesions that are painful by palpation and may extend deeply and over large areas. They frequently result in painful lesions, exudative sinus tracts and tissue destruction.[7]

Conglobate acne is a rare but severe form of acne found most commonly in adult males with lesions usually on the trunk, upper limbs and buttocks. In contrast to ordinary acne, facial lesions are less common and it can persist to the sixth decade of life. Conglobate acne is characterised by multiple grouped comedones amidst inflammatory papules, tender, suppurativa nodules which may coalesce to form sinus tracts. Extensive and disfiguring scarring frequently results.

Because acne treatment varies with severity and type, grading and classification of acne plays an important role in decision making for clinicians treating patients with acne. More than 25 different grading systems for the assessment of acne severity have been published[3] including the Global Acne Grading System (GAGS) and the Comprehensive Acne Severity System (CASS). Global grading is based on photographic templates and descriptive text of primary lesions which is practical and clinically relevant but more

subjective, and therefore less reliable, than a system of lesion counting.[8] Consequently there is a lack of consensus on the best acne classification and grading systems and no system is universally accepted as a global standard.[3]

2.1.3 Epidemiology of Acne

2.1.3.1 Prevalence

Acne is estimated to affect 9.4% of the global population, making it the eighth most prevalent disease worldwide[9] and the single most common reason persons aged 15 to 45 years visit a dermatologist in the US.[10]

2.1.3.2 Age

The most common age for acne to occur is between 12 and 25 years[11] but it persists into the 20s and 30s in around 64% and 43% of affected individuals respectively.[12] The prevalence of adults aged > 25 years with acne is increasing and, in this age group, acne is more frequent and persistent in females.[13,14]

2.1.3.3 Gender

The World Health Organisation states that while most people are born either male or female (biological sex), they are taught appropriate behaviours for males and females (gender norms). For the purpose of this study, gender and sex will be used as synonyms.

Self-reported studies have found higher rates of acne and lower rated quality of life in females[15] which may be due to females being more sensitive to the presence of acne, particularly in its milder forms. Of all people whose principal diagnosis or reason for a visit to a registered physician is acne, 65% are female.[10,16]

However a notable difference has been shown between the age distribution of males and females seeking medical attention for acne with two thirds of males being aged < 20 years while most females are aged > 20 years. This suggests females aged > 20 years perceive acne as a continuing problem requiring medical treatment.[10]

2.1.3.4 Severity

In New Zealand a 2004 self-reported survey of 9570 adolescent students in Years 9 – 13 at school found 67% of students reported acne and 14% reported ‘problem acne’.[17] Globally moderate to severe acne affects 15 to 20% of young people[12] and is most common in teenagers post-puberty, with boys most frequently affected, particularly with more severe forms of the disease.[9]

In the 2004 New Zealand self-reported survey of adolescent students, females, Pacific, and older students reported 'problem acne' more frequently than other groups.[17] However this may not reflect severity diagnosed with clinical assessment by a trained examiner as studies using clinical examination usually rate acne as more severe in males than in females.[11]

2.1.3.5 Ethnicity

It is unclear if ethnicity is associated with acne[12] as the pathogenesis and clinical appearance of lesions is the same in patients of all ethnicities. In a global study across women in four cities (London, Los Angeles, Rome and Akita in Japan), the prevalence of acne was found to be 37% in African Americans, 32% in Hispanics, 30% in Asians, 24% in Caucasians and 23% in Continental Indians leading authors to conclude acne prevalence and sequelae were more common in those people of darker skin types.[18] On a per capita basis in the US between 1990 and 1997 there were 29 visits to a physician for the treatment of acne per thousand people per year that were Asian/Pacific Island, 20 that were white and 8.8 that were Black.[16]

Dark skinned people are more susceptible to increased pigmentation and the melanocyte responses to inflammation, which can complicate acne by leading to post-inflammatory hyperpigmentation, may be of greater concern to the patient than the acne itself. The increased risk of dyspigmentation and keloidal or hypertrophic scarring in more severe cases, means under-treatment in dark skinned patients should be avoided.[19,20]

2.1.4 Treatment of acne

This section will summarise the recommended treatments for the different severities of acne. Although I am not specifically addressing medication adherence in this study, it is worth noting that a clinic in the United Kingdom (UK) that analysed acne treatment adherence found the major reasons for missing treatment given by the patients were being fed up, forgetful or too busy. Smoking cigarettes and drinking alcohol were shown to reduce medicine adherence.[15]

2.1.4.1 Treatment of mild acne:

Mild acne can usually be successfully treated with topical treatments obtainable in New Zealand without prescription.[21] Suitable topical agents available in New Zealand in October 2015 include:

- Antiseptic washes with triclosan or benzoyl peroxide (Acnederm wash, Benzac AC Wash, Dalacin T Prewash, Oxy Daily Skin Wash)
- Mild salicylic acid preparations to exfoliate and unplug the follicles (Neutrogena Oil-free Acne Wash and many others)
- Benzoyl peroxide cream/lotion/gel (PanOxyl Acne Gel, Brevoxyl Cream, Clearasil Ultra Acne Cream, Benzac AC Gel). There seems to be no additional benefit to using higher strengths of benzoyl peroxide and lower strengths such as 2.5% have fewer side effects.[22]
- Azelaic acid (Skinoren cream, Acnederm medicated lotion, Azclear Action Lotion)
- Hydrogen peroxide in stabilised cream (Crystacide, Crystaderm)
- Tea tree oil products[23,24]

Topical agents for mild acne that require a prescription include:

- Antibiotics, such as clindamycin solution (ClindaTech) which is best used with benzoyl peroxide or azelaic acid to reduce the chance of antibiotic resistance.
- Retinoids i.e. tretinoin (ReTrieve), adapalene (Differin)

Combination prescription topical treatments including clindamycin / benzoyl peroxide (Duac) and adapalene/benzoyl peroxide gel (Epiduo) have the highest strength of recommendation for their use.[7]

Many acne patients notice an improvement in their acne over summer[25] and ultraviolet light has been used in the management of acne although concerns around skin cancer risk have limited this use.[21] Lights and lasers[26] including phototherapy with intense pulsed light (IPL) have been found to be safe and effective[27] for mild to moderate acne when oral medications are unhelpful or unsuitable.

2.1.4.2 Treatment of moderately severe acne

Management of moderately severe acne may include the topical agents described above and at least three to six months oral medication. Suitable oral medications include:

- Antibiotics such as minocycline, lymecycline, doxycycline or erythromycin although concomitant use of different topical and systemic antibacterials is not

recommended due to an increased likelihood of the development of bacterial resistance.[28] When oral antibiotics are discontinued, control should be maintained long term by continuing topical therapy.

- In females, oestrogens and antiandrogens such as Diane 35/Estelle 35 and/or spironolactone are helpful, particularly if there are signs of hyperandrogenism. This excessive male sex hormone (testosterone) may lead to signs of seborrhoea, acne, hirsutism, irregular menstruation, obesity and balding.

- For resistant or persistent moderately severe acne, oral isotretinoin may be more suitable.[21]

2.1.4.3 Treatment of Severe Acne

Severe acne primarily requires treatment with oral agents, often with isotretinoin. Other treatments may also be used such as high dose oral antibiotics for six months or longer, topical treatments such as azelaic acid, benzoyl peroxide and adapalene, and antiandrogens in females.

Table 1 shows the Strength of Evidence for acne treatments that are available in New Zealand based on the European Guidelines for the Treatment of Acne published in 2012.[7]

Table 1: Strength of Recommendations for Acne Treatments

Strength of Recommend-ation	Comedonal Acne	Mild to Moderate papulopustular acne	Severe papulopustular/ moderate nodular acne	Severe nodular/conglobate acne
High	-	Adapalene and Benzoyl Peroxide (Epiduo) or Clindamycin and Benzoyl Peroxide (Duac)	Isotretinoin	Isotretinoin
Medium	Topical Retinoid	Azelaic acid or Benzoyl Peroxide or topical retinoin or systemic antibiotic + adapalene	Systemic antibiotic + adapalene or systemic antibiotic + azelaic acid or systemic antibiotic + adapalene and BPO	Systemic antibiotics + azelaic acid
Low	Azelaic acid or benzoyl peroxide	Blue light or systemic antibiotic + benzoyl peroxide or systemic antibiotic + azelaic acid or systemic antibiotic + adapalene +	Systemic antibiotics + benzoyl peroxide	Systemic antibiotics + benzoyl peroxide or systemic antibiotic + adapalene or systemic antibiotic + adapalene + benzoyl peroxide (Epiduo)

		benzoyl peroxide		
Alternatives for female patients	-	-	Hormonal antiandrogens + topical treatment or Hormonal antiandrogens + systemic antibiotics	Hormonal antiandrogens + systemic antibiotics

2.1.5 Acne Recurrence

Acne is considered a chronic disease because acne lesions typically recur for years.[29] Following successful acne treatment, maintenance therapy in the form of topical retinoids has been shown to minimise the potential for relapse and recurrence.[29] This approach is now replacing the traditional use of oral antibiotics as maintenance therapy and repeat courses of the same antibiotic in the event of relapse.[30]

The relapse rate after treatment with isotretinoin is the lowest of all acne therapies.[7] Even so, long-term remission is achieved only in 70 to 80% of patients having a single isotretinoin course.[31]

The significant factors for relapse of acne following oral isotretinoin treatment include:

- Stopping isotretinoin before acne has completely cleared
- Macrocomedonal disease
- Severity of acne
- Excessive seborrhoea after finishing isotretinoin
- Smoking
- Younger age, under 14 years
- Older age, particularly women over 25 years
- Polycystic ovarian syndrome.[31]

2.2 Isotretinoin

Isotretinoin is a retinoid first approved for oral use in New Zealand on 29 September 1983.[32] It is the *cis* configuration of tretinoin which is the acid form of vitamin A.[33]

2.2.1 Who can prescribe isotretinoin in New Zealand

Isotretinoin should be prescribed only by physicians who are experienced in the use of systemic retinoids and understand the risk of teratogenicity if used during pregnancy.[34] Risk management programmes have been implemented in different countries since the introduction of isotretinoin. However audits of their success have shown a lack of compliance and isotretinoin-exposed pregnancies have occurred despite these recommendations for use.[35–38] No pregnancy prevention programme (PPP) has been in place in New Zealand.

The National Health Index (NHI) code is a unique patient identifier that is assigned to every person who uses health and disability support services in New Zealand.[39] The NHI provides information about gender, age, ethnicity and socioeconomic status of individual patients.

Prior to 1 March 2009 funded oral isotretinoin was available in New Zealand only for prescriptions written by vocationally registered dermatologists many of whom did not have easy access to NHI codes to include on prescriptions. Consequently only 60% of isotretinoin prescriptions at this time can be linked to other health data although linear extrapolation has been previously used to allow for missing NHIs.[1] Pregnancies did occur while women were taking isotretinoin under the dermatologist-only restricted isotretinoin prescribing. In the year to June 2008, 39 terminations of pregnancy (TOPs) in the six months following isotretinoin prescription were identified in New Zealand.[40]

While funded access was available only through a dermatologist's prescription it was recognised that people living in more deprived areas (as defined by the New Zealand Deprivation Index (NZDep)) were less likely to use isotretinoin, as were Maori and Pacific people.[1]

2.2.2 Changes to the Access of Isotretinoin

The Pharmaceutical Management Agency (PHARMAC) is the government entity charged with managing the publicly funded pharmaceutical budget in New Zealand. From 1 March 2009 PHARMAC added isotretinoin to the Special Authority System in

which a prescriber requests government subsidy of a drug for a particular person where the prescribing meets specific criteria. At this time PHARMAC widened funded access so vocationally registered general practitioners (GPs) and nurse practitioners were also able to make applications for a Special Authority to prescribe isotretinoin for their patients.

The criteria for Special Authority approval of isotretinoin requires vocationally registered dermatologists, GPs or nurse practitioners working in a relevant scope of practice to have up to date knowledge of the safety issues around isotretinoin and for female patients to have been counselled and to understand the risk of teratogenicity. Among other criteria ensuring other acne treatments are given an adequate trial first or are contraindicated, prescribers must exclude the possibility of pregnancy before commencing isotretinoin treatment and female patients must be informed that they must not become pregnant during treatment and for one month after the completion of treatment.[41]

Once a Special Authority application is approved for this patient, a Special Authority number is issued that is valid for one year after which it may be renewed. Renewals are also valid for one year and there is no limit on the number of renewals as long as all criteria are met. Once the Special Authority number is issued, any prescriber may prescribe isotretinoin for the patient as long as the number and its expiry date are quoted on the prescription. If the prescription is presented to a pharmacy without this number, a pharmacist can check the Special Authority database online and complete these details.

2.2.3 Indications for Oral Isotretinoin

The main indication for oral isotretinoin therapy is severe forms of acne or acne at risk of permanent scarring that is unresponsive to other therapy especially when the lesions involve the trunk.[34] These severe forms of acne include nodulocystic acne, which is characterised by many nodules and cysts, and acne conglobata where interconnecting abscesses and sinuses (channels under the skin) can result in unsightly scars and groups of large macrocomedones and cysts filled with smelly pus.[24]

While registered in New Zealand only for use in acne, dermatologists may rarely also use isotretinoin for other skin conditions such as hydradenitis suppurativa[1] and rosacea.[42]

Other off-label uses of oral isotretinoin include psoriasis, pityriasis rubra pilaris, condyloma acuminatum, granuloma annulare, Darier's disease, systemic cutaneous lupus erythematosus and non-melanoma skin cancer.[43]

2.2.4 Mechanism of Action

The fundamental aspects of cell development where retinoids exhibit influence are in cell growth, differentiation, morphogenesis and apoptosis (a form of programmed cell death). Retinoids also inhibit tumour promotion and malignant cell growth, exert immune-modulatory actions and alter cellular cohesiveness through their ability to influence gene transcription and other mechanisms.[31]

Isotretinoin is a synthetic stereoisomer of all-trans retinoic acid (tretinoin). When taken orally isotretinoin has a marked effect in severe forms of acne and is the only drug available that impacts all four pathogenic factors associated with acne.[44]

1. Isotretinoin reduces sebaceous gland size (up to 90%) by arresting the cell cycle and inducing apoptosis within the sebaceous gland.

2. This decreases the proliferation of sebaceous gland cells, disturbing their differentiation and suppressing sebum production.[44,45]

3. Although isotretinoin does not directly affect *Propionibacterium acnes,* its inhibitory effect on sebum production leads to an alteration of the follicular microclimate, so that an indirect fall in the number of *Propionibacterium acnes* bacteria occurs.[45]

4. In addition phospholipase, an enzyme that hydrolyses cell membrane phospholipids to generate inflammatory mediators such as arachidonic acid, is down-regulated by isotretinoin.[46]

It is estimated isotretinoin affects over 500 genes; 300 being up-regulated and 200 down-regulated. However the pattern of gene expression changes over time with an initial induction of apoptosis and cell cycle arrest, particularly in the sebaceous gland, followed by the skin adopting a wound-healing-like pattern, with subsequent repair and remodelling.[31]

After just one week of treatment, distinctly different patterns of gene expression can be identified in people taking isotretinoin and hundreds of genes are changed by eight

weeks. Most genes that are down-regulated are lipid and sterol (cholesterol) metabolising enzymes within the sebaceous glands. The majority of genes that are up-regulated affect structural proteins of the extracellular matrix such as collagens, fibulin and fibronectin. This is thought to lead to the known effects of retinoids in rebuilding extracellular matrix and may explain isotretinoin's beneficial effects during acne resolution.[46]

The size and structure of sebaceous glands returns to pre-treatment levels as early as two months after cessation of therapy and the rate of return is faster with lower doses of isotretinoin. Despite this, isotretinoin induces permanent remission of acne in the majority of cases.

Oral retinoids have no effect on male fertility[47] but isotretinoin is a recognised teratogen in females and causes a spectrum of congenital anomalies in more than 35% of exposed infants. The mechanism is thought to involve cytotoxic peroxyl free radical generation by metabolism with prostaglandin synthase resulting in toxic effects on the initial differentiation and migration of neural crest cells. The critical period of exposure is believed to be two to five weeks after conception.[45,48,49] Isotretinoin has also recently been found to have a significant negative effect on ovarian reserve based on hormonal parameters, ovarian volume and follicle count in women with acne.[50,51]

2.2.5 Dosing

The recommended dose regimen in New Zealand for treatment with oral isotretinoin is to commence treatment at a dose of 10 – 20 mg/day for three to five months [53] and to continue until all acne lesions have resolved. Treatment should then be continued for a further two to four months to reduce the risk of relapse and help with the resolution of acne scarring.[31] Based on clinical response and the tolerance of side effects, the second stage of treatment may be at a reduced dose such as 5 – 10mg per day.

In some cases, acne actually worsens with initial isotretinoin therapy and, in patients with severe nodulocystic acne, an initial flare can result in permanent scarring. For this reason, it is recommended patients are started at the lower end of the recommended range then for treatment to be escalated as tolerated.[54,55]

Clinical efficacy appears to be similar regardless of whether the dose is taken once or twice daily, but dividing the dose may reduce the incidence of adverse effects.[56] Food

doubles the bioavailability of isotretinoin and the manufacturers recommend taking it with food.

This dose regimen has been recommended in New Zealand since studies published since 2006 have demonstrated the effectiveness of lower doses of isotretinoin with fewer side effects.[53,57,58,59] However these recommendations are cited in some international journals as still requiring long-term follow-up to authenticate this approach.[60]

Dosing guidelines written prior to these studies, and still in place in the Medsafe Datasheets and New Zealand Formulary in 2015, recommend doses based on body weight such as 500 micrograms/kg daily (in one to two divided doses) initially for two to four weeks, increased if necessary to 1 mg/kg daily for 16–24 weeks.[34,61] These doses are still in use in some countries[62] although the recommended doses of isotretinoin are lower in Canada and the UK than in the United States (US).[63]

The authors of dosage studies have advocated total cumulative doses from 120 mg/kg to greater than 220mg/kg per course to increase remission rates and prevent relapse.[64,65] However treatment endpoints varied widely and the evidence base for this recommendation is now challenged.[66] It is now believed a shorter length of sebaceous gland suppression is more likely to explain instances of relapse in lower daily doses.[31] Consequently it is now recommended the dose and duration of oral isotretinoin should relate to clinical response with lower cumulative doses required for clearance of mild to moderate acne, and higher for more severe acne.[66]

National dispensing data in New Zealand from July 2011 to June 2012 showed there were two most commonly prescribed isotretinoin doses. These were at 10 – 20 mg per day which was the dose for 63% of dispensings but there was a second most commonly prescribed dose of 80 – 90 mg per day which was prescribed in a further 22% of prescriptions. This usage in 2011 represented an average daily dose of 42 mg isotretinoin.[53] It was not clear whether the 10 – 20 mg peak represented a deliberate strategy for low dose prescribing or whether prescribers were using lower doses in response to adverse effects.

2.2.6 Adverse Effects

With the exception of teratogenicity, most of the common adverse effects of oral isotretinoin are dose related and become more common and more severe with higher

doses.[53] It is this predictable and dose-related nature of the adverse effects that has led to the development of varied dose regimens.[54] At the higher dose of 1mg/kg per day, 98% of patients report adverse effects while at doses below 0.25mg/kg per day, 50% of patients report no adverse effects at all, and in those who do, the effects are significantly less severe.

Most frequently observed are symptoms associated with hypervitaminosis A. Dryness of the mucosa is generally most troublesome on the lips (chelitis), but may also occur on the nasal mucosa (leading to epistaxis), pharyngeal mucosa (leading to hoarseness) and dryness of the vaginal and/or anal mucosa. Dryness of the eyes can cause conjunctivitis and reversible corneal opacities. These mucocutaneous reactions can generally be managed with regular use of lip balms, moisturisers or artificial tears as needed.

Temporary, reversible increases in liver transaminases may be significant in some patients[67] and have occasionally made dose reduction or discontinuation necessary.[34] Increases in serum triglyceride and cholesterol levels, as well as decreases of high-density lipoprotein (HDL), have been observed in patients taking oral isotretinoin particularly at high dosages and in predisposed patients. A risk of pancreatitis should be considered with triglycerides above 9 mmol/litre.[61] However these changes are also dose related and return to normal on reduction of the dosage or withdrawal of the medicine.[34]

Several blood dyscrasias have been reported with oral isotretinoin treatment including thrombocytopenia, thrombocytosis, neutropenia, leucopoenia, decreases in white and red blood cell counts including anaemia and an increased sedimentation rate.[34,61,68] Although no causal relationship has been established, elevated fasting blood sugars have been reported and new cases of diabetes have been diagnosed during isotretinoin therapy.[34]

Isotretinoin is eliminated almost exclusively by hepatic metabolism and biliary excretion.[34] In patients with severe renal insufficiency it is recommended treatment be started at a lower dose;[34] one case report exists of suspected renal impairment induced by isotretinoin.[69]

To address these potential risks and to ensure blood lipids, liver enzymes and blood cell counts remain within the healthy range during treatment, guidelines state patients

should have a full blood count, fasting lipids, renal and liver function tests performed within one month prior to being prescribed isotretinoin, after one month of treatment and three monthly during treatment.[70,71] In patients who have diabetes, or are at high risk of developing diabetes, frequent determination of blood glucose levels is also recommended.

Because abnormalities occur rarely[72] and isotretinoin is usually prescribed for a younger population with generally good health, if follow-up monitoring at least once during a 16 to 30 week course of treatment suggests no significant changes from a healthy baseline, repeated blood count, creatinine and glucose tests need only be repeated as clinically required.[72,73] In New Zealand between July 2011 and June 2012, 47% of patients had all three baseline tests (blood count, liver enzymes and lipids) as recommended, but just 13% of patients had all three tests both before and at least once during their course of isotretinoin treatment.[73]

Night blindness is the most common and earliest symptom of vitamin A deficiency and isotretinoin inhibits retinal enzymes needed to synthesise vital components for normal vision. Isotretinoin-induced night blindness has been reported and some groups of patients, such as pilots, vehicle drivers and defence force personnel who require intact night vision, should be aware of this rare but potential side effect.[74]

2.2.6.1 Teratogenicity

The Australian categorisation system for prescribing medicines in pregnancy rates isotretinoin as a Category X medicine indicating it has such a high risk of causing permanent damage to the foetus that it should not be used in pregnancy or when there is a possibility of pregnancy.[61] Of infants affected with isotretinoin embryopathy, over 70% will have anotia/microtia (undeveloped or underdeveloped external ear) as illustrated in Figure 2. Over 25% of affected infants will have a smaller lower jaw (micrognathia) and >10% will have cleft palate. Heart defects are seen in about 40%, thymic defects in >30% of affected infants and retinal or optic nerve abnormalities in nearly 20%. Defects of the central nervous system, such as microencephaly, are also seen.

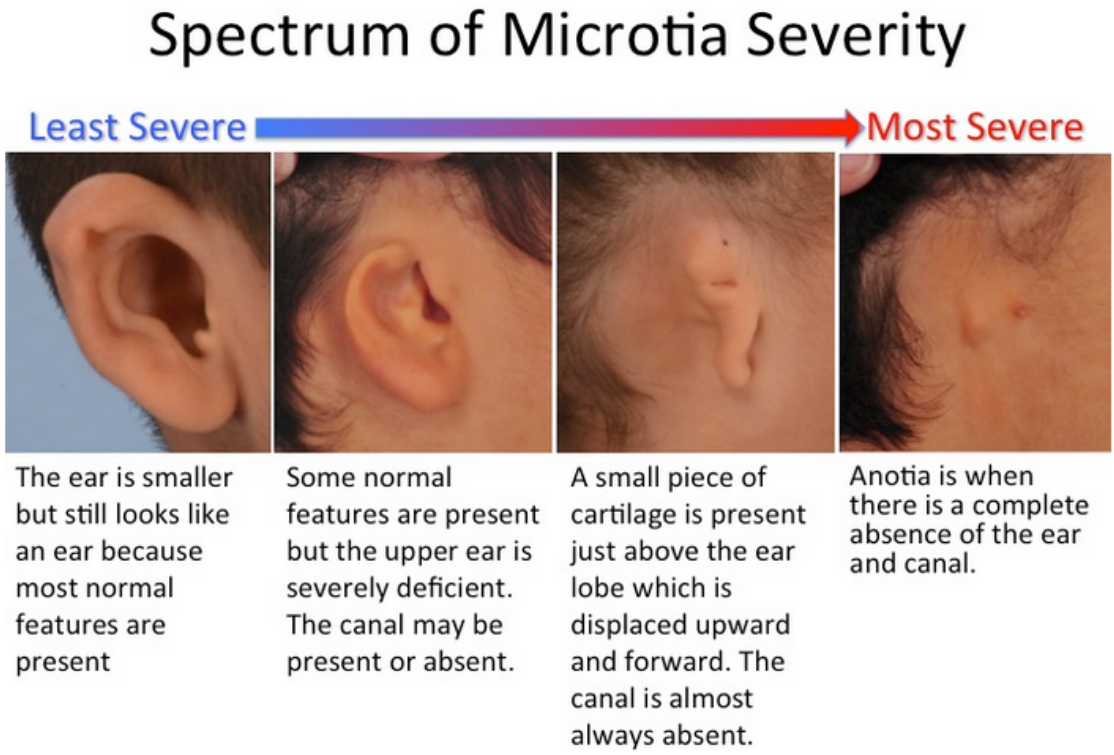


Figure 2: Spectrum of Microtia Severity

Source: Derderian, Christopher A., Spectrum of Microtia Severity. [cited 2015 Sep 20]. http://www.drderderian.com/microtia/

Cognitive performance problems are seen even among children who have no evident structural defects, with 40% of all children prenatally exposed to isotretinoin having impaired learning abilities.[75] Isotretinoin also increases the risk for miscarriage or stillbirth which occurs in up to 40% of exposed pregnancies and there is a doubled risk of premature birth.[76] Current recommendations are that women must also avoid pregnancy for four weeks after stopping isotretinoin**.**

2.2.6.2 Depression

There are data to suggest a possible association between isotretinoin treatment and depression in 1-11% of patients, and evolving evidence that isotretinoin affects the neurotransmitters of the brain that have been known to cause depression.[77]

However suicidal ideation is more common in people with severe compared with mild acne[12] and this is the group more likely to have treatment with isotretinoin. Some studies have suggested oral isotretinoin is not a risk factor for depression[78] and that it actually produces an improvement in symptoms of anxiety and/or depression in patients with mild to moderate acne.[46,57]

Consequently it is recommended healthcare providers discuss with their patients the risk benefit ratio of isotretinoin treatment and monitor at each visit for the development of signs of any negative effect on mood.[77]

2.2.6.3 Inflammatory Bowel Disease

Inflammatory Bowel Disease (IBD) has been frequently reported in people taking isotretinoin but large studies have failed to show an increased risk of IBD among isotretinoin-exposed patients[79–81], no causal relationship has been documented[34,54,77,79,82–84] and in the US reporting has been recognised as disproportionally initiated by attorneys.[85]

IBD is idiopathic and chronic intestinal inflammation seen as ulcerative colitis and Crohn's disease. IBD can occur at any age but the peak incidence is between ages of 15 and 30 years - the same peak as for the use of isotretinoin. There may also be a link in that both IBD and nodulocystic acne are inflammatory conditions.[77]

Tetracyclines, including minocycline and doxycycline that are used to treat acne, have been associated with an increased risk of IBD. However it does not appear that use of isotretinoin itself increases the risk of IBD with antibiotics.[77,79] This is important because many patients who are treated with isotretinoin have previously tried and failed other acne treatments such as oral antibiotics, and the decision support tool in New Zealand will not recommend oral isotretinoin for mild or moderate acne unless previous treatment has failed. However it remains important for clinicians to ask about personal or family history of IBD and to be alert to any possible early symptoms prior to starting and during treatment with isotretinoin.

2.2.6.4 Drug Interactions

A reduction in the effects of isotretinoin has been reported following significant alcohol intake[86] but the clinical significance of alcohol intake during isotretinoin treatment is not known. The metabolism and pharmacokinetics of isotretinoin does not appear to be influenced by ethanol.[87]

Tetracycline antibiotics should not be given with isotretinoin due to increased risk of intracranial hypertension.[54,61] Where tetracyclines have been trialled to treat patients' acne, they must be withdrawn before commencing oral isotretinoin.

Vitamin A supplements should also be avoided during systemic isotretinoin treatment due to additive toxic effects and because case reports exist of a condition similar to vitamin A (retinol) overdose.[54]

The pharmacokinetics and ovulation suppressant effect of combined hormonal oral contraceptives are not affected by isotretinoin[88] but it is unclear if isotretinoin affects the reliability of oral progestogen-only contraceptives so they are not generally considered reliable enough for use with isotretinoin.[61]

2.3 Trends in Isotretinoin Usage in the Literature

This section will describe the known differences in the use of isotretinoin by age, gender, ethnicity, socio-economic level and prescriber type both in New Zealand and globally.

2.3.1 Age Differences

There is little published data available to demonstrate the most common age for isotretinoin treatment in New Zealand. During 2005-6 in South Africa the median age of female patients using isotretinoin was 21 years and 18 years in male patients. This finding was a decrease in age from a previous study done almost a decade before.[89] Data collected in 2001 when isotretinoin was only funded through dermatologists in New Zealand showed teenagers reported difficulty accessing treatment for acne in increasing numbers during the teenage years with a peak at age 16 years.[17] However other studies have shown that when treatment is provided, younger patients are more likely to be adherent with their acne treatment which may impact the safe and successful outcomes of treatment in various ages.[15]

2.3.2 Gender Differences

Consideration of isotretinoin prescribing patterns by gender is important because the teratogenic side effects of isotretinoin that are present only in females may influence its use in this population group. If this risk creates a significant barrier to prescribing and use in females, greater isotretinoin use in males might be expected over and above the increased male tendency to more severe acne.[11]

Difficulty accessing treatment for acne (not just isotretinoin) has been more commonly reported by female than male students[17] and adherence to acne treatment is better in

females.[15] Although per capita acne visits in the US are higher for women, men are 1.7 times more likely than women to receive isotretinoin during an acne visit.[16] Prior to 2000 in the US female patients consistently received 50% of isotretinoin prescriptions[63] while in South Africa during 2005-6 female patients received 57% of isotretinoin prescriptions.[89] To date, no published data has shown the use of isotretinoin by gender in New Zealand.

2.3.3 Ethnicity Differences

The European ethnic group is the largest in New Zealand with 74% of the population identifying themselves with one or more European ethnicities in the 2013 census. This had increased from 68% in the 2006 census but the increase was attributed to fewer people identifying themselves as 'New Zealander' in 2013. Other ethnic groups increased in size from the 2006 Census to 2013 Census including:

• Mäori – 14.9% of the population in 2013 which was up from 14.6% in 2006

• Asian – 11.8% of the population which had increased from 9.2% in 2006

• Pacific peoples – 7.4% of the population which was up from 6.9%

• Middle Eastern/Latin American/African (MELAA) – 1.2% of the population which had increased from 0.9%. [90]

Current consensus on the management of acne is that there is no difference in recommended treatment for people of different ethnicities.[12] The survey of 6299 New Zealand adolescent students who had acne in 2001 found students of Pacific or Maori ethnic groups reported difficulty accessing treatment (not just isotretinoin) more frequently than New Zealand Europeans.[17] In the US between 1990 and 1997 isotretinoin was also less frequently prescribed to blacks than whites[16] and cost, patient and provider biases were thought to be potential factors as well as racial differences in severity of acne.

Similarly during the year ending June 2008, Maori and Pacific people were less likely to use isotretinoin than those of Other ethnicity (mainly New Zealand European)[1] and during the year July 2011 to June 2012 since access was widened to include GPs and nurse practitioners, this showed no obvious change.[91]

2.3.4 Socio-economic Differences

Medicine adherence to acne treatment is increased in employed people and people who do not need to pay for their acne prescriptions. However these groups of people also have a lower Dermatology Life Quality Index (DLQI) reflecting less impact on quality of life from their acne.[15] Being employed and not paying for prescriptions were characteristics associated with increased medicine adherence and a lower DLQI.

In New Zealand in 2008 when isotretinoin was funded only when prescribed by a dermatologist, there was a clear linear association between the use of isotretinoin and deprivation level. People from the least deprived quintile were more than two and a half times as likely to access isotretinoin compared with people from the most deprived quintiles. Relative ethnic inequalities compounded the socio-economic differences, so that Maori and Pacific people in the least deprived quintile used isotretinoin at about half the rate of other ethnicities in the most deprived quintile.[1] The only study to review this data since the 2009 change in access to funded isotretinoin showed no obvious change to this association between the highest and lowest decile socioeconomic groups between July 2011 and June 2012 in New Zealand.

2.3.5 Differences by Prescriber Type

A 2008 analysis of isotretinoin prescribing arrangements around the world showed Australia, Denmark, Ireland, Sweden and the UK restricted prescribing to dermatologists only. The US, Canada, Argentina, Brazil, France, and Italy permitted any medical doctor to prescribe isotretinoin while in Bolivia, Mexico and Venezuela isotretinoin was an over-the-counter purchase with no prescription necessary. In the most recent European data available, published in May 2015 from six European databases in Norway, the Netherlands, Tuscany/Emilia Romagna regions of Italy, Wales and the rest of the UK, isotretinoin is still mainly prescribed by specialists.[92]

In the US in 2010 dermatologists represented 72% of the prescribers registered in iPLEDGE [93] and they are shown to initiate over 80% of isotretinoin prescriptions.[16,94] In the US, dermatologic mid-level providers such as physician assistants and nurse practitioners also prescribe isotretinoin. In 2010, 18% of the prescribers registered in iPLEDGE were these non-physicians.[93]

In South Africa during 2005 and 2006, dermatologists prescribed 67% of isotretinoin prescriptions and GPs 29%. A 2011 study in the UK found isotretinoin could be

purchased from 42 out of 50 e-pharmacy websites without a valid prescription and when orders were placed on eight of these sites, seven arrived, all without any patient information leaflet.[95]

Prior to March 2009, all funded oral isotretinoin prescriptions in New Zealand were written by dermatologists but one previous study showed that from July 2011 to June 2012 58% of isotretinoin prescriptions originated from a GP.[91]

2.3.6 International Systems to Prevent Pregnancy

The greatest challenge in treating sexually active women of child-bearing potential with isotretinoin is contraceptive adherence and human error. The Pearl index, a measure of contraceptive failure for various methods of contraception, is generally less than 2.5 per 100 women at one year[96] meaning that women using one form of contraception during isotretinoin treatment may typically still conceive at around this rate.

2.3.6.1 United States of America

In the US in 2001, 5% of women aged 15-44 years had an unintended pregnancy but pregnancy rates during isotretinoin use are lower (0.3%).[97] The United States Food and Drug Administration (FDA) has the authority to require a Risk Evaluation and Mitigation Strategy (REMS) from manufacturers to ensure the benefits of a drug or biological product outweigh their risks.[98] Essentially, a REMS is a safety strategy to manage a known or potentially serious risk associated with a medicine and to enable patients to have continued access to those medicines by managing their safe use.[99]

Since its approval in the US in 1982, several REMS have attempted to minimise foetal exposure to isotretinoin. The first US PPP was established in 1988 targeting prescribers and patients but reports of foetal exposure and the number of prescriptions among women of reproductive age continued to increase. In 2002 the System to Manage Accutane-Related Teratogenicity (SMART) was implemented with more stringent monitoring of pregnancy and prescription dispensing. The number of prescriptions for isotretinoin declined after SMART (and its generic equivalents) but there was not a substantial decrease in reports of foetal exposure. Consequently a more rigorous and uniform risk management program named iPLEDGE was implemented in 2006.
The computer-based iPLEDGE programme requires more rigorous monitoring of contraceptive use with monthly pregnancy tests and healthcare providers, wholesalers, pharmacies and patients must all register in the programme. It allows real-time linkage

of pregnancy-test results for verification prior to isotretinoin dispensing.[100] Following introduction of this programme the number of prescriptions decreased but resumed to pre-iPLEDGE levels within 10 months. Similarly a small increase in the proportion of female patients, particularly younger women, concomitantly using isotretinoin and contraceptives after the introduction of iPLEDGE was not maintained over time.[94] The pregnancy rate among isotretinoin users in the US with iPLEDGE was estimated at 2.7/1000 treatment courses and this was not significantly different from the previous SMART.[38] Concerns over the high rates of prescriptions for isotretinoin that were denied due to failure to comply with iPLEDGE guidelines have prompted development and analysis of new patient support programmes.[101]

2.3.6.2 Europe

As the result of a European-wide review of isotretinoin use in 2003, a European Union (EU) PPP was agreed and, when surveyed in 2011, a PPP was in force in 21 of the 27 member countries. Over 80% of these countries incorporated the following seven required elements of the formal EU review[38,97]

1.Isotretinoin is contraindicated in pregnant women and should only be initiated in women of reproductive age who understand the teratogenic risk and the need for regular follow-up.

2.Use of effective contraceptive measures from 4 weeks before isotretinoin initiation until 4 weeks after treatment discontinuation. At least one and preferably two complementary forms of contraception including a barrier method should be used.

3.Pregnancy testing should be performed before, during and 5 weeks after discontinuation of isotretinoin.

4.Isotretinoin should only be prescribed by or under the supervision of a physician with experience in the use of systemic retinoids.

5.Prescription should be limited to 30 days of treatment and continuation of treatment requires a new prescription.

6.Dispensing of isotretinoin should occur within a maximum of 7 days after prescribing.

7.Educational programmes for healthcare professionals including prescribers and pharmacists, and patients are in place to inform them about the teratogenic risk and to create awareness of the PPP.

Despite this implementation, isotretinoin-exposed pregnancies occurred[102] and so some European countries required additional pregnancy prevention measures. Consequently the consistent approach agreed in 2003 is no longer the universal approach for Europe.[97]

The British Association of Dermatologists conducts regular audits of isotretinoin prescribing by its members. The most recent 2014 audit showed over 91% of women prescribed isotretinoin had signed the acknowledgement of PPP information indicating they had received appropriate information.[103]

2.3.6.3 Other Countries

In Canada, any physician can prescribe isotretinoin and a PPP requires female patients to sign an informed consent form and to agree to use at least two concurrent methods of birth control, one of which must be an oral contraceptive pill, during isotretinoin treatment.

In Israel, only dermatologists can prescribe isotretinoin and all female patients must sign a consent form and agree in writing to use effective contraception during treatment and for an additional month afterwards.

2.4 Termination of Pregnancy Trends

This section will describe TOP numbers and trends in New Zealand and other countries as background to the consideration of TOPs following isotretinoin use.

2.4.1 New Zealand

All legal TOPs in New Zealand must be reported to the Abortion Supervisory Committee including TOPs that are not publicly funded. The data presented in this section, therefore is sourced from a more complete dataset than the National Minimum Dataset (NMDS) which includes only publicly funded TOPs.

2.4.1.1 Trends in Number of TOPs

Of the 13,137 induced TOPs in 2014, New Zealand residents accounted for 11, 971 (91%), non-residents for 955 (7%) and 211 (2%) were not stated. The total number of

induced legal TOPs in New Zealand has been steadily declining since 2007 as illustrated in Figure 3.

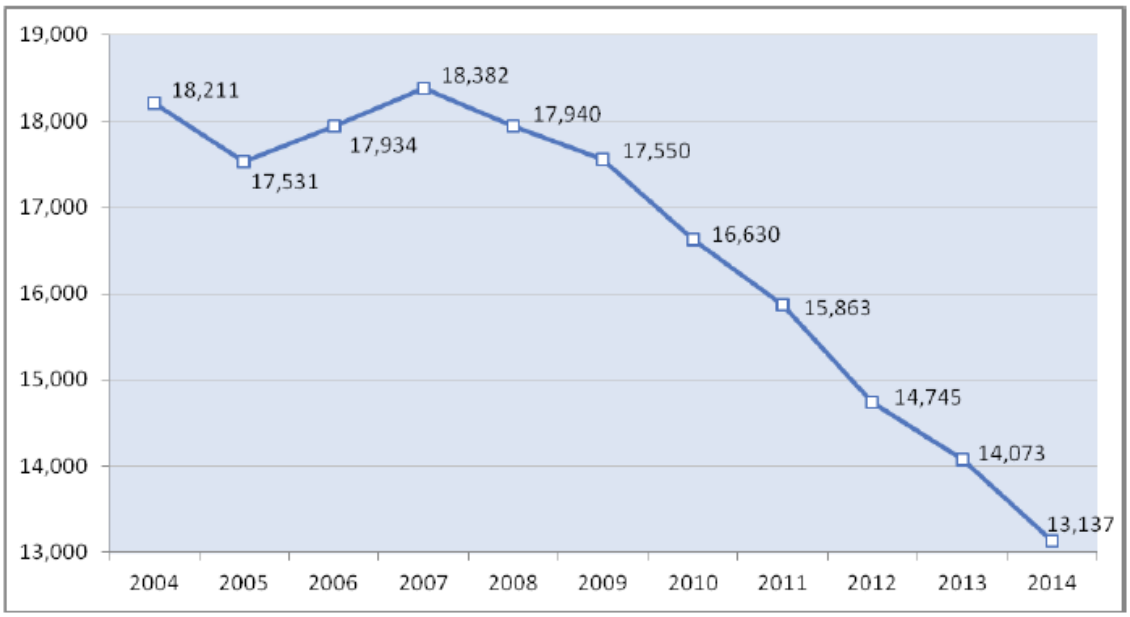


Figure 3: Total Number of Induced Legal TOPs 2004 - 2014 in New Zealand

Source: Abortion Supervisory Committee, 2015, [cited 2016 Apr 10]. http://www.justice.govt.nz/tribunals/abortion-supervisory-committee/annual-reports/asc-annual-report-2015

The general TOP rate is the number of TOPs per 1,000 of the mean estimated population of women aged 15 – 44 years. The TOP rate in New Zealand from 2004 to 2014 reflected the total number of induced TOPs during this time declining from 20.1 in 2007 to 14.4 in 2014.

2.4.1.2 Trends in Ethnicity of Women having TOPs

In absolute numbers more European women have TOPs than any other ethnicity which would be expected as 74% of New Zealanders identify as European.[90] Ethnic differences in TOP rates per 1,000 women have been identified in New Zealand as shown in Figure 4. People can belong to more than one ethnic group so the number of TOPs by ethnicity sum to more than the total number of TOPs.

The TOP ratio is the number of TOPs per 1,000 known pregnancies. Known pregnancies include live births, stillbirths and induced TOPs combined, but do not include miscarriages. Asian women have previously had the highest TOP rates and ratios[104] of all ethnic groups in New Zealand. However the TOP ratio for Asian women

has declined consistently since 2007 and in 2014 the number of TOPs per 1,000 known pregnancies for Asian women was similar to the ratios for Maori or Pacific women.

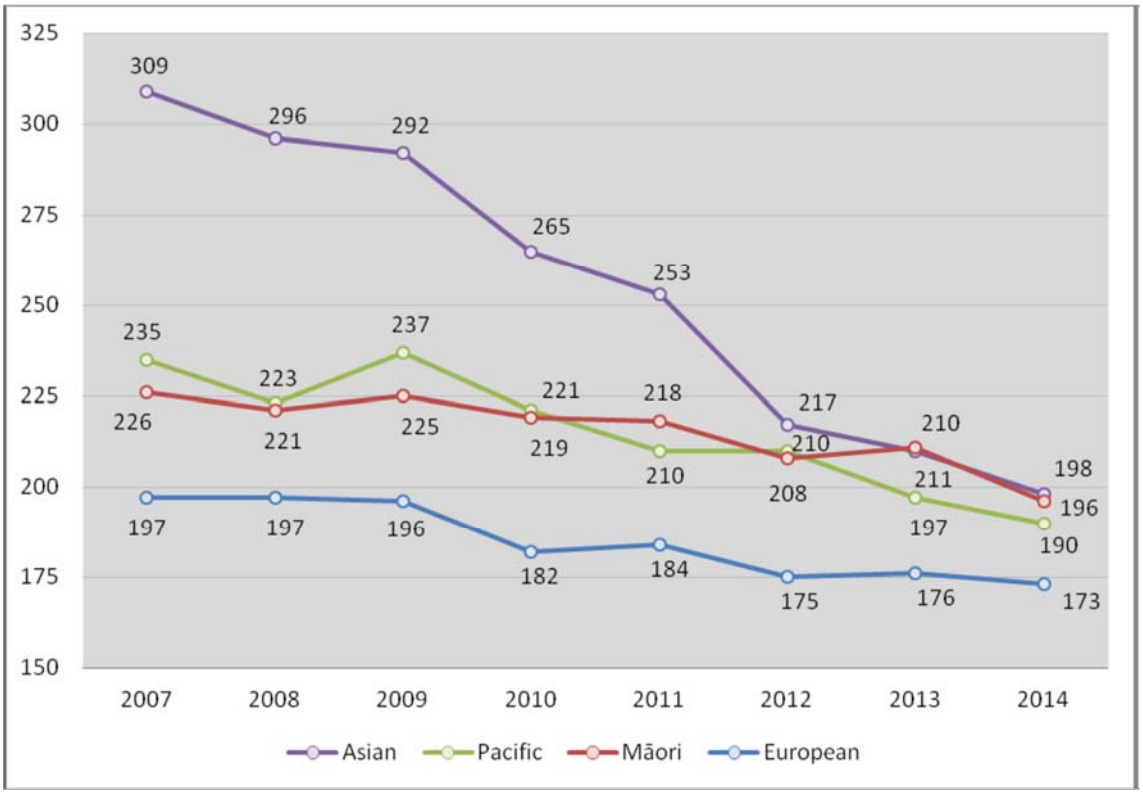


Figure 4: Induced TOPs in New Zealand by Ethnicity Ratio 2007 – 2014

Source: Abortion Supervisory Committee, 2015, [cited 2016 Apr 10]. http://www.justice.govt.nz/tribunals/abortion-supervisory-committee/annual-reports/asc-annual-report-2015

The Abortion Supervisory Committee of New Zealand noted the inclusion of long acting subcutaneous contraception to the already available intra-uterine devices may be one factor contributing to the steady decline in the number of TOPs.[105]

2.4.2 TOP Trends in Other Countries

The general TOP rate in low fertility countries has declined slightly in countries where data were available as shown in Table 2. Of the countries where data were available in 2012, Sweden had the highest TOP rate with 20.7 TOPs per 1,000 women aged 15 – 44 years. England, New Zealand and Wales had the second highest rate with just over 16 while Norway and Denmark have a slightly lower rate with around 15 TOPs per 1,000 women aged 15 – 44 years. Data available for 2011 showed France and the US also very similar to New Zealand, England and Wales in that year at around 17 TOPs per 1,000 women aged 15 – 44.

Table 2: TOP Rate in Low Fertility Countries 2002-2013[106]

	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013
Australia	20.3	19.7	19.3	-	-	-	-	-	-	-	-	-
Denmark	14.1	14.7	14.4	14.5	14.4	14.8	15.5	15.8	15.8	15.1	14.8	14.3
England/Wales	16.2	16.6	16.9	17.0	17.5	17.9	17.6	17.0	17.1	17.2	16.4	16.5
Finland	11.0	10.8	11.3	11.1	10.8	10.7	10.7	10.7	10.5	10.9	10.4	10.4
France	16.8	16.5	17.1	16.7	17.5	17.4	17.1	17.3	17.6	17.4	17.3	-
Germany	7.8	7.7	7.8	7.5	7.4	7.3	7.3	7.2	7.3	7.4	7.4	7.2
Netherlands	8.7	8.5	8.7	8.6	8.6	8.6	8.7	8.8	8.7	8.7	8.5	8.5
New Zealand	19.9	20.8	20.2	19.3	19.6	20.1	19.7	19.3	18.2	17.4	16.3	15.6
Norway	14.8	15.1	15.3	15.1	15.4	16.1	17.0	16.4	16.2	15.6	15.3	14.7
Scotland	11.1	11.6	11.8	12.0	12.5	13.1	13.3	12.4	12.2	11.9	11.9	11.2
Sweden	19.6	20.2	20.0	20.2	20.6	21.0	21.3	20.8	20.9	20.9	20.7	-
US	20.5	20.2	19.7	19.4	19.9	19.4	19.4	18.5	17.7	16.9	-	-

Source: Statistics New Zealand, 2015, [cited 2016 Apr 10].
http://www.stats.govt.nz/browse_for_stats/health/abortion/AbortionStatistics_HOTPYeDec14.aspx

2.5 Isotretinoin, Pregnancy and TOP

This section will examine isotretinoin-exposed pregnancies in New Zealand before looking at what is currently known about the global situation.

2.5.1 New Zealand

Exposure to isotretinoin during pregnancy is not grounds for TOP in New Zealand.[107] The most commonly cited grounds for TOP are danger to the mental health of the woman. In 2014, 97.3% of all induced legal TOPs were for this reason with the second most common grounds for TOP significantly fewer: ‘handicapped child and mental danger’ accounting for 0.9% and ‘mental and physical health danger’ accounting for 0.8% of all TOPs.

TOP rates following isotretinoin in New Zealand need to be interpreted against the background of the previously described overall declining TOP rate. In 2011 Moodie et al[40] reported on TOPs occurring while using isotretinoin in New Zealand and stated it would be important to regularly review these data to ensure the widening of funded

access did not have any unexpected negative effects on the health of the population. These researchers showed a linear correlation between all legal TOPs and deprivation quintiles with individuals from the most deprived areas having three times more TOPs than women living in the least deprived areas in the year ending June 2008.

Therefore if the change in funding increased access to isotretinoin for women who already had more TOPs, it was anticipated that the rate of TOPs per patient treated could increase, in addition to wider use. This meant the absolute number of TOPs following isotretinoin dispensings would logically increase.[40]

2.5.2 Europe

In 2009 a questionnaire was sent to all 25 EU member states plus Norway and Iceland, and 22 responded. Since isotretinoin has been available in these countries, 393 pregnancies exposed to isotretinoin have been reported, 143 since the introduction of the EU PPP in 2003. Five countries reported no exposed pregnancies and one country did not have data available. The most reported pregnancies in one country were 289 including 65 which followed implementation of the current PPP.[97]

Looking specifically at the Netherlands where a population based study of all isotretinoin exposed pregnancies $\geq$ 16 weeks in the Netherlands from 1 January 1999 to 1 September 2007 showed 2.5 pregnancies per 10 000 were exposed to isotretinoin despite the PPP and 60% of these women started isotretinoin while already being pregnant.[38] This figure did not include spontaneous abortions before 16 weeks or elective TOPs so these results probably underestimate the number of isotretinoin-exposed pregnancies and their consequences. The PPP was implemented in 1988 in the Netherlands and this nationwide study showed a lack of full compliance to the isotretinoin PPP.

2.5.3 Other Countries

Between 1984 and 2002 in Canada there was an annual pregnancy rate during isotretinoin treatment of 32.7 per 1000 person-years of treatment. Of women who became pregnant while on isotretinoin, 84% had a TOP, 3% had a spontaneous abortion, 2% had trauma during delivery resulting in neonatal deaths and 10% had a live birth. Among the live births, one (11%) had a congenital anomaly of the face and neck.[108]

2.6 Clinical Decision Support for Isotretinoin Prescribing

2.6.1 Decision-making software for primary care

Decision-making software has been made available in many areas of healthcare to provide clinicians with additional support beyond referencing guidelines in both chronic and acute care settings. Decision support tools are becoming ubiquitous throughout New Zealand primary care with goals to improve access, quality of care and cost-effectiveness.[109] However their use has rarely been carefully evaluated to determine if they achieve these aims or improve outcomes.

Best Practice Advocacy Centre (BPAC) electronic decision support modules are used by 76% of general practices and 85% of GPs.[110] International evidence of whether point-of-care decision support improves patient care has been equivocal. While benefit of improved processes of care and guideline adherence has been shown, there has been little assessment of risks (costs and interruption to workflow) or benefit to patient outcome. Systematic reviews of the decision support literature conclude there is a shortage of well-designed trials of decision support that provide assessments of their effectiveness in changing patient outcomes as well as in changing clinician behaviour.[111–113]

There has been no research investigating the impacts of any chronic care BPAC Decision Support modules on clinical behaviour and patient outcomes in New Zealand, although the use following transient ischaemic attack/stroke has been shown to improve guideline adherence, safely reduce treatment cost, achieve positive user feedback, and may reduce cerebrovascular and vascular event risk.[110]

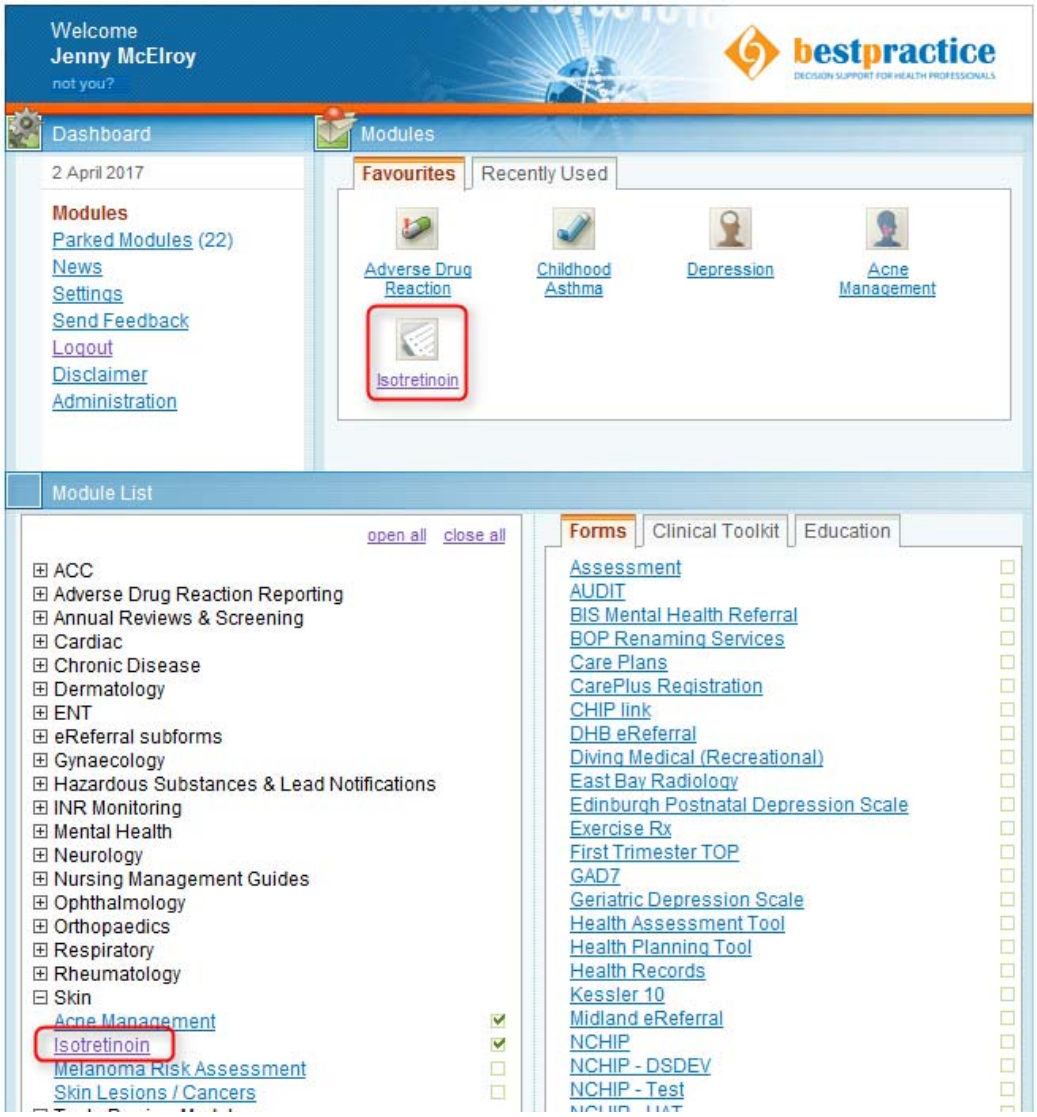
Decision making software for primary care may aid GPs who had previously not prescribed isotretinoin to recognise when isotretinoin treatment is appropriate and promote treatment initiation rather than referring for specialist review as previous funding regulations had required. One of the benefits of decision support tools is that they are inherently educational, providing GPs with guideline based advice which can be applied to the management of future patients and improve management skills over time.[110]

2.6.2 Acne/Isotretinoin Decision Support in New Zealand

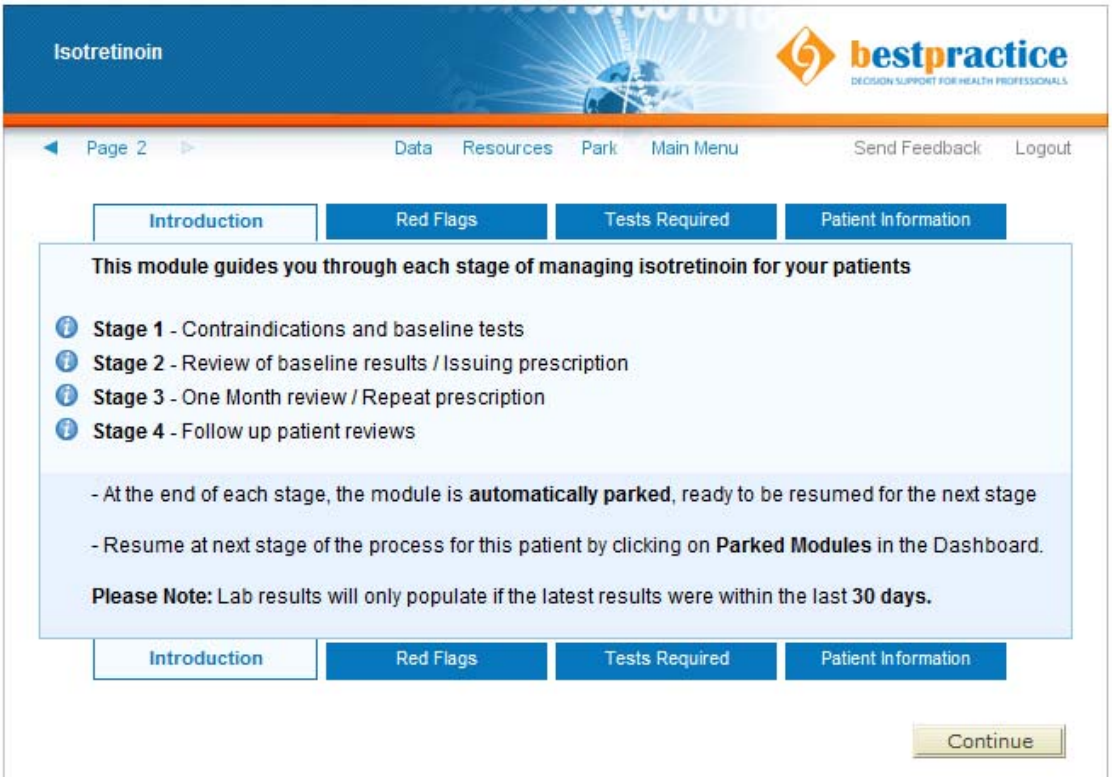
At the time of the isotretinoin funding change, PHARMAC funded the development of an electronic decision support tool for the treatment of acne. This tool was made available to primary care clinicians throughout New Zealand to support the safe prescribing and use of isotretinoin. This tool was developed and supplied by BPAC CS Ltd and was fully integrated with the main practice management systems in use. The tool required a patient's NHI code to be recorded and allowed clinicians to easily access information on contra-indications, dosage guidelines, recommended laboratory tests, patient consent forms and patient information sheets relevant to their current patient.

2.6.2.1 Use of the BPAC Isotretinoin Decision Support Tool

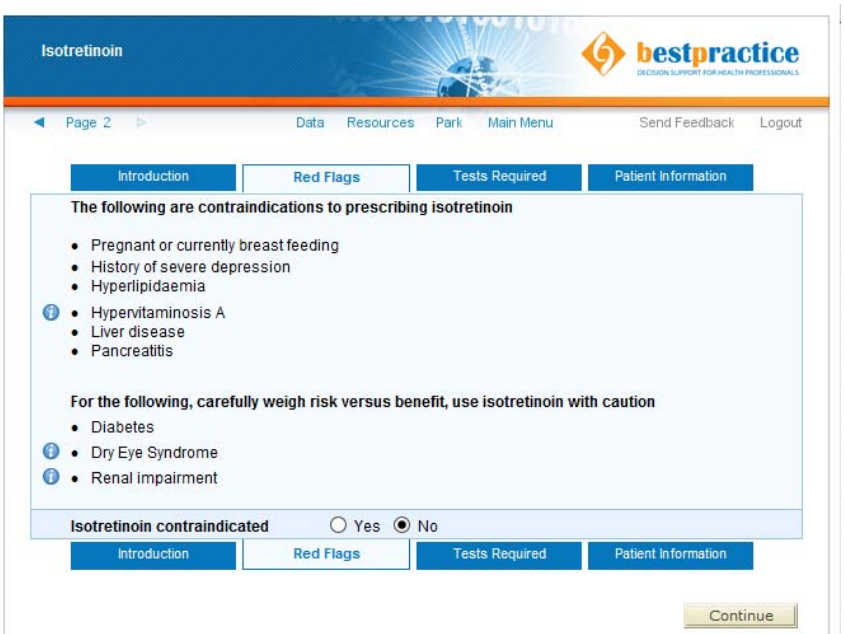
The decision support tool is a Web-based software programme accessed via an icon on the GP's Practice Management System. The icon takes the User to the BPAC Main Menu, from where they choose the Acne Management or Isotretinoin module.



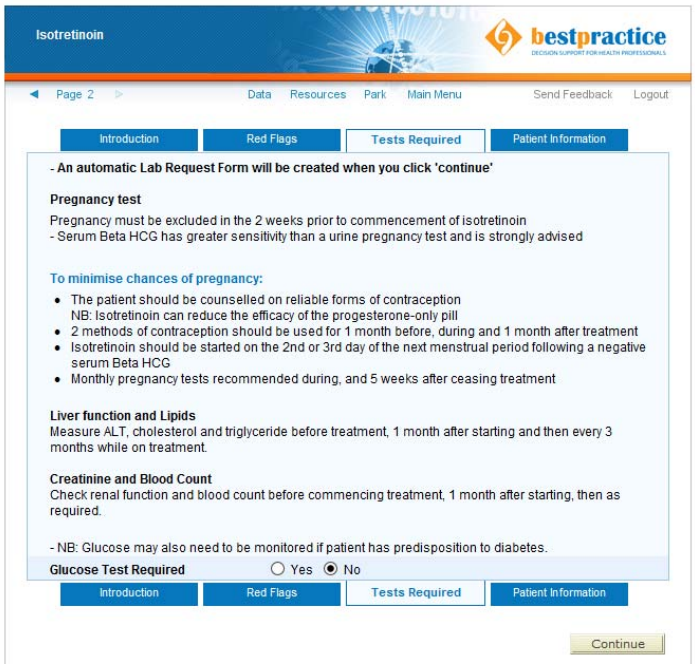
This will take the User to the landing page for the Module which is the Introduction tab and explains the process for prescribing and managing patients on isotretinoin.



The User then clicks the next tab to view the Red Flags. The contraindications and situations where prescribing must only be done with caution are described on this page. The blue information icons provide Users with further information on some of the terms used in the module: For example the hover next to Dry Eye Syndrome states:



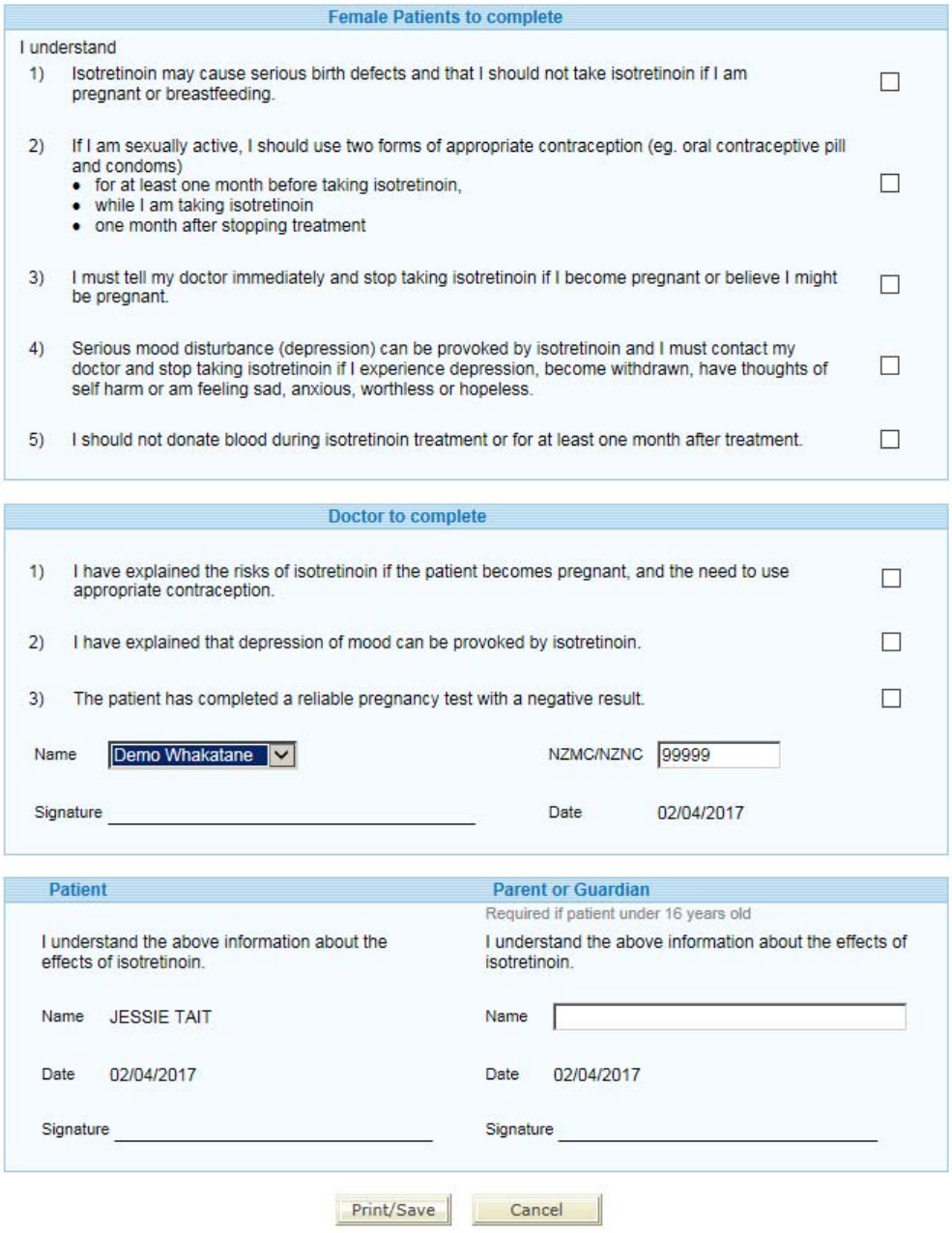
If the clinican confirms isotretinoin is not contra-indicated, they move to the Test Required tab where an explanation of the recommended tests required is available. This page is gender specific and so includes the Pregnancy test information for all female patients. The Glucose Test Required question defaults to No with a note that glucose testing may be required for patients predisposed to diabetes.



The final tab is a Patient Information tab. On this tab there is a link to the Isotretinoin Consumer Medicine Information sheet and a gender-specific patient information sheet. These can be printed and given to the patient.

There is also a gender specific Patient Consent Form which includes the teratogenicity and contraceptive issues for female patients. Clicking on the link to the Isotretinoin Patient Consent Form will produce a copy of a gender specific form, with the first three statements only included for female patients.

A copy of the blank form as sighted by the User will be written back to the Patient Management System if it is opened, however many GPs chose to print the form, sign it personally and have the patient do so as well. This was then routinely scanned back into the patient record.



Female Patients to complete

I understand

1) Isotretinoin may cause serious birth defects and that I should not take isotretinoin if I am pregnant or breastfeeding. ☐

2) If I am sexually active, I should use two forms of appropriate contraception (eg. oral contraceptive pill and condoms)
- for at least one month before taking isotretinoin,
- while I am taking isotretinoin
- one month after stopping treatment ☐

3) I must tell my doctor immediately and stop taking isotretinoin if I become pregnant or believe I might be pregnant. ☐

4) Serious mood disturbance (depression) can be provoked by isotretinoin and I must contact my doctor and stop taking isotretinoin if I experience depression, become withdrawn, have thoughts of self harm or am feeling sad, anxious, worthless or hopeless. ☐

5) I should not donate blood during isotretinoin treatment or for at least one month after treatment. ☐

Doctor to complete

1) I have explained the risks of isotretinoin if the patient becomes pregnant, and the need to use appropriate contraception. ☐

2) I have explained that depression of mood can be provoked by isotretinoin. ☐

3) The patient has completed a reliable pregnancy test with a negative result. ☐

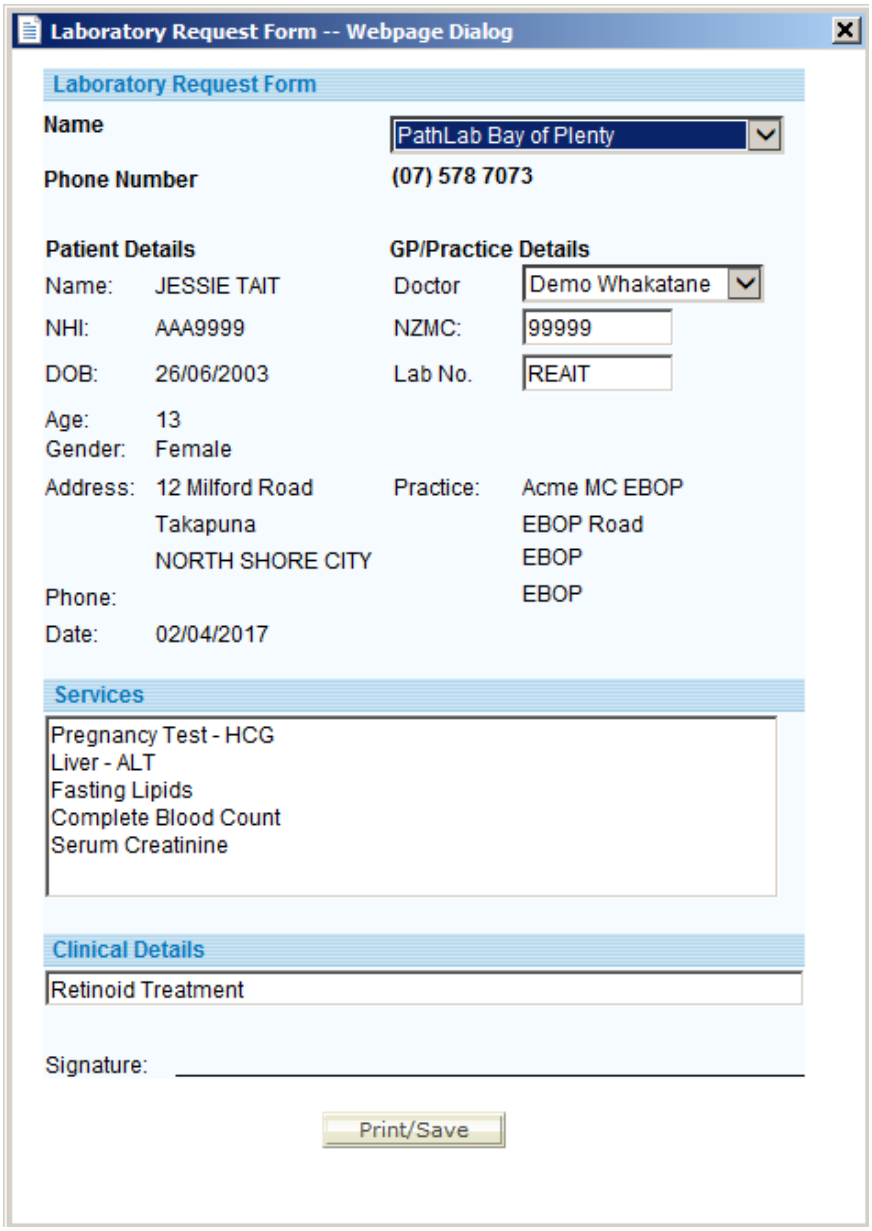
Name Demo Whakatane NZMC/NZNC 99999

Signature _____ Date 02/04/2017

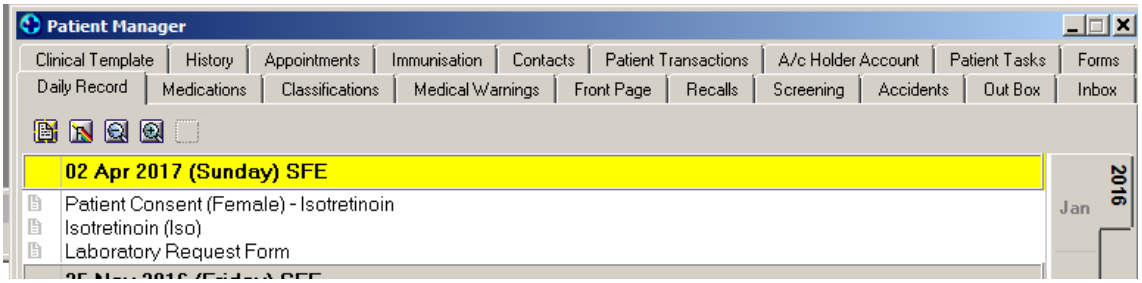
Patient	Parent or Guardian
	Required if patient under 16 years old
I understand the above information about the effects of isotretinoin.	I understand the above information about the effects of isotretinoin.
Name JESSIE TAIT	Name
Date 02/04/2017	Date 02/04/2017
Signature _____	Signature _____

Print/Save Cancel

Having completed the Consent Form, clicking 'Print/Save' would automatically create a copy of the Laboratory Request Form. The GP would choose the appropriate Laboratory service and had the option of adding or removing any of the laboratory services requested before printing.



Upon completion of these steps, a copy of each action is written back to the patient record.



The technical aspects involved in processing these steps take 40 seconds. However the module is likely to stimulate appropriate discussion around the use of a teratogenic agent requiring two forms of contraception in females and some blood monitoring which may extend the consultation time.

The decision support tool aids clinicians in ensuring they have considered the contra-indications and appropriate laboratory tests while having easy access to patient information and appropriate consent forms in a readily-accessible format during the consultation.

In the only randomised controlled trial involving a BPAC decision support tool to date, GP feedback was positive about the Stroke/TIA tool with all 63 GP respondents saying they would use that tool at least some of the time[114]. In that study comments included statements such as "allows quick evidence-based decision making in a short consultation and no need to duplicate notes or letters."

Other electronic information sources have been available to clinicians in some regions in addition to the BPAC Decision Support tool but these have not been nationally available or integrated with a unique patient identifier to provide information tailored to specific patients. For example, in Canterbury HealthPathways in 2014 there were 154 searches on the word *isotretinoin* and 960 on the words *severe acne* (personal communication: User Documentation Specialist, Streamliners, 2015). Primary care clinicians in the Canterbury region who had access to HealthPathways may not routinely have felt the need to access the BPAC tool for decision support when prescribing isotretinoin.

One significant difference with the BPAC Isotretinoin Decision Support tool is the way it involves patients. As has been pointed out by dermatologists, closer adherence to guidelines by clinicians alone will not always avoid isotretinoin-exposed pregnancies.[115] Whereas many similar decisions support tools promote guideline adherence for clinicians, this module involves patients with a consent form and information leaflets that can be easily printed and personally discussed with the patient during the consultation. These active methods of disseminating information have been empirically shown to be more effective than passive strategies such as printed pamphlets or websites used alone.[116] As patient compliance with recommendations around contraception and pregnancy-prevention is essential to successful management of

teratogenic risk, the value of the module is increased by its provision of opportunities to enhance these processes.

This study provides a retrospective comparison of rates of TOP and exposed birth in patients cared for by clinicians who accessed the tailored decision support tool for their isotretinoin patients, to rates of TOP and exposed birth for patients of clinicians who did not. This will be the first whole population audit for the use of a decision support tool in New Zealand and the first to examine differences in the rate of an undesirable patient outcome following the use of decision support when prescribing a specific drug.

2.6.3 New Zealand National Collections

The Ministry of Health collects data from different parts of the health sector in New Zealand and makes this available to stakeholders and researchers via National Collections. The national collections of health and disability data provide health information on doctor's visits, laboratory and pharmaceutical claims, immunisations, cancer, maternity, hospital events, mortality, mental health, and medical warnings. These data are linked by the universal use of the NHI code to identify individuals and the encounters they have with the health system.[117]

2.7 Research Objectives

The overall aim of this study is to understand the prescribing trends and adverse maternity outcomes of isotretinoin in New Zealand from 1 March 2007 to 1 March 2015. The study will answer the following research questions.

1) Has the use of funded isotretinoin in New Zealand from 1 March 2007 to 1 March 2015 changed with regard to age, gender, ethnicity, and deprivation level?

The null hypothesis is that there is no significant change in the use of oral isotretinoin by age, gender, ethnicity or deprivation level between 1 March 2007 and 1 March 2015.

2) Has widened access to funded isotretinoin correlated to a change in the rate of TOP following isotretinoin dispensing and the number of potentially isotretinoin-exposed live births in New Zealand?

The null hypothesis is that there is no significant difference in the rate of TOP following isotretinoin dispensing and the number of potentially isotretinoin- exposed live births in New Zealand women since widened access was introduced on 1 March 2009.

The study will also identify the proportion of isotretinoin prescribers who were dermatologists or GPs or others in each year during the study period from 1 March 2007 until 1 March 2015.

3) Is there a difference in the rate of TOP following isotretinoin or the number of potentially isotretinoin-exposed live births between different prescriber types in New Zealand from 1 March 2007 to 1 March 2015?

The null hypothesis is that there is no significant difference in the rate of TOP following isotretinoin or the number of potentially isotretinoin-exposed live births by prescriber type in New Zealand from March 2007 to March 2015.

4) Is there a difference in the rate of TOP following isotretinoin or the number of potentially isotretinoin-exposed live births between women whose prescriber accessed the BPAC decision support tool for them and women whose prescriber did not?

The null hypothesis is that there is no significant difference in the rate of TOP following isotretinoin or the number of potentially isotretinoin-exposed live births between those women whose prescriber used a decision support tool for them and those whose prescriber did not.

3 Research Design, Data Sources and Methods

This study examined retrospective annual isotretinoin usage data from 1 March 2007 to 1 March 2015. The Ministry of Health's Information Group operates the National Collections for health and disability information in New Zealand. These data are available to researchers and the public on request[118] and provided one data source for this study. In addition to the National Collections, the BPAC Isotretinoin Decision Support module usage information was also obtained from BPAC CS LP. Descriptive analysis was used to interpret the findings from matching these data sources. The datasets were given the following names:

1. Isotretinoin Usage Dataset
2. Maternity Dataset 1
3. Maternity Dataset 2
4. Decision Support Usage Dataset
5. Decision Support and Maternity Data matched

This chapter will describe how the data from these sources was cleaned and matched for the purposes of this study. Further details of the methods employed and examples to illustrate the processes implemented are shown in appendix A and B. Figure 5 illustrates how the datasets were cleaned to identify the maternity events relevant to this study.

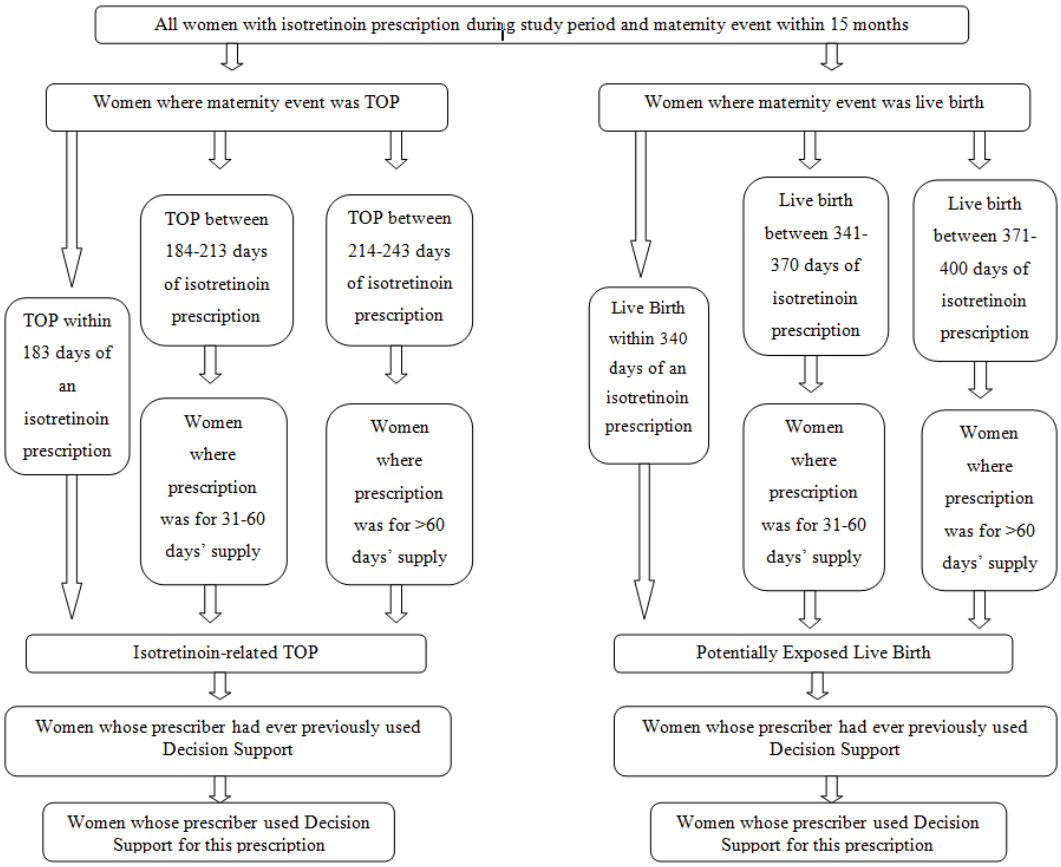


Figure 5: Method of Cleaning Datasets to Determine TOPs and Potentially Exposed Live Births in Women Dispensed Isotretinoin where Decision Support was used

3.1 Isotretinoin Dispensing and Demographic Data Sources

NHI codes were used as the unique patient identifier to link the information from the different data sources in this study. The NHIs in the various sources were consistently encrypted by the Ministry of Health enabling a detailed picture of health information for each encrypted NHI to be determined. NHI codes were only ever visible to researchers in encrypted form.

The national dataset used to provide isotretinoin dispensing data in this study was the Pharmaceutical Collection. This data warehouse contains prescription claim and payment information from community pharmacists' subsidy claims and is jointly owned by the Ministry of Health and PHARMAC.[118] Demographic data such as age, gender, ethnicity and socioeconomic status (deprivation quintile) of people in this study were

obtained from the Primary Health Organisation (PHO) Enrolment Collection. The ethnic code groups used in the National Collection are shown in Table 3.

Table 3: Ethnic Code Groups used in the National Collections[119]

Ethnic Code Group	Ethnic Code Group Description
1	European
2	Maori
3	Pacific Peoples
4	Asian
5	MELAA*
6	Other Ethnicity

*MELAA = Middle Eastern/Latin American/African

If people identified more than one ethnicity, they were allocated to a single ethnic group, based on the prioritised order of Mäori, Pacific, Asian and European/Other.[120] Socioeconomic deprivation in New Zealand is defined by the New Zealand Index of Deprivation based on the area of residence of an individual. It is based on census variables such as income, home ownership, employment, qualifications, family structure, housing, access to transport and communications.[121] The Index represents the relative socio-economic deprivation of an area and does not directly relate to individuals.

3.1.1 Cleaning Isotretinoin Usage Data

1. **Isotretinoin Usage Dataset**

The data provided for each record in the Isotretinoin Usage Dataset and its source is described in Table 4. This dataset was sorted and filtered to analyse the gender, ethnicity, age, deprivation quintile and the number of days' supply at each isotretinoin dispensing. The isotretinoin usage data was provided in an excel spreadsheet covering all dispensings of isotretinoin from March 2007 to February 2015 (inclusive). It was provided with a separate worksheet for the isotretinoin dispensings in each year ending 1 March. Because some individuals had isotretinoin dispensed in more than one year, their NHI code was included on more than one of these annual tabs, meaning the total number of people dispensed isotretinoin could not be totalled across the annual worksheets. Consequently data analyses on the total data set were carried out using Structured Query Language (SQL).

Table 4: Data Fields and Data Source contained in Isotretinoin Usage Dataset

Data Source	Data Field	Definition
Pharmaceutical Collection	Date Dispensed	Date of Each Dispensing
Pharmaceutical Collection	Chemical Name	Isotretinoin
Pharmaceutical Collection	Formulation Name	Cap 10mg or 20mg
Pharmaceutical Collection	Encrypted NHI	
Pharmaceutical Collection	Number of Items	
Pharmaceutical Collection	Provider Type	Medical or other
Pharmaceutical Collection	Repeat Sequence Number	To indicate if this was the first, second (etc) time isotretinoin was dispensed off one prescription
Pharmaceutical Collection	Dose	The number of capsules per dose
Pharmaceutical Collection	Days' Supply	Days of Isotretinoin Treatment supplied
Pharmaceutical Collection	Sex Code	
Pharmaceutical Collection	Patient Age at Dispensing	
PHO Enrolment Collection	Ethnic Group Code	Level 1 Ethnic Code
PHO Enrolment Collection	Deprivation Quintile	

These data were used to determine the number of patients dispensed isotretinoin in each year from 1 March 2007 to 2015. The change in total numbers of patients from one year to the next was then used to determine the rate of change in the number of patients accessing funded isotretinoin for each year before and after 1 March 2009.

Rates of TOP and exposed live birth per prescriber-type were calculated from the number of females who had isotretinoin prescribed by each prescriber-type during the study period.

3.2 Maternity Data Sources

The national collection used to provide maternity and birth information in this study was the NMDS of hospital events. The NMDS includes public and private hospital discharge information including coded clinical data for inpatients and day patients.[117] It

provides statistical, demographic and clinical information about publicly funded maternity services that are recorded in Diagnosis Related Groups. These Diagnosis Related Groups are derived from the International Statistical Classification of Diseases and Related Health problems, 10th Revision, Australian Modification (ICD-10-AM codes) which is the clinical coding classification developed by the World Health Organisation and used in New Zealand hospitals.[122] Chapter XV of the ICD-10-AM codes includes all codes relating to pregnancy, childbirth and the puerperium (O00-O99) with pregnancies with abortive outcomes covered by O00-O08. Chapter XXI includes codes relating to factors influencing health status and contact with health services (Z00-Z99) with codes for outcome of delivery covered by Z37 as a category intended for use as an additional code to identify the outcome of delivery on the mother's record.[122]

All TOPs carried out in public hospitals, as well as TOPs that are publicly funded and carried out in private hospitals, are reported in this way. These data were delivered from the Ministry of Health for prescriptions dispensed for the period 1 January 2007 to 30 June 2015. However the study period was prescriptions dispensed for the years ending 1 March 2008 through to 1 March 2015.

This study obtained information on the number of days' supply of isotretinoin provided at each dispensing. Consequently where more than 30 days of isotretinoin was dispensed, the extra period of supply extended the time during which a TOP may be linked to isotretinoin, or a subsequent live birth is potentially exposed to isotretinoin.

3.2.1 Cleaning Maternity Data

This section will describe the process of identifying the relevant data required to achieve the aims of this study and how it was cleaned from the datasets received.

Pregnancies with abortive outcomes are classified as O00 – O08 ICD-10-AM Version for 2016. Codes of O00 to O03 are ectopic pregnancies, hydatidiform moles, other abnormal products of conception and spontaneous abortion. Codes O04 to O07 are used for TOPs while O08 are complications following TOP, ectopic and molar pregnancy. This meant the data I received will allow future analysis of the adverse maternity outcomes following isotretinoin prescriptions, but this analysis did not form part of the current study. In this study, the maternity outcomes coded O00 to O03 were not analysed.

Previous analysis has assumed that isotretinoin prescriptions within the six months preceding TOP suggest a possible link between isotretinoin use and TOP. This period was considered sufficient to take into account prescription length, one month post medication period, time to awareness of pregnancy and time to organise TOP.[40]

The current recommendation is that women should not become pregnant for at least a month following the end of isotretinoin treatment. People encountering health services in circumstances related to reproduction are classified as Z30 – Z39 in ICD-10-AM Version for 2016. Codes starting from Z37 are used as additional codes to identify delivery outcomes on the mothers' records such as single live birth, single stillbirth, and twins both live born.

To identify the relevant events for my study from the maternity data provided, I filtered the data to the following subsets for individual analysis:

- TOPs within six months (183 days) of an isotretinoin prescription where the prescription quantity was less than 31 days' supply
- TOPs within seven months (183 + 30 = 213 days) of an isotretinoin prescription where the prescription quantity was 31 - 60 days' supply
- TOPs within eight months (183 + 60 = 243 days) of an isotretinoin prescription where the prescription quantity was more than 60 days' supply
- Live Births within 340 days of an isotretinoin prescription where the prescription quantity was up to 30 days' supply (30 days treatment period + 30 days break + 280 days pregnancy)
- Live Births within 370 days of an isotretinoin prescription where the prescription quantity was 31 - 60 days' supply (60 days treatment period + 30 days break + 280 days pregnancy)
- Live Births within 400 days of an isotretinoin prescription where the prescription quantity was more than 60 days' supply (90 days treatment period + 30 days break + 280 days pregnancy)

For the purposes of filtering data for this study, any prescription for less than 31 days' supply was treated as 30 days' treatment period. For any period of supply 31-60 days' supply, the treatment period was filtered as if it had been for 60 days' supply. Any

period of supply >60 days was filtered as if it had been for 90 days' supply. The small numbers of related dispensings that fell into this category meant each was then individually examined to understand the potential for isotretinoin exposure.

2. Maternity Dataset 1

Maternity Dataset 1 was separated into calendar years for the period from 1 March 2009 to 31 December 2014 and matched isotretinoin prescriptions with females who had a maternity event within 12 months. The data had 3 worksheets for each calendar year and is shown in Table 5.

Table 5: Data Source and Data Fields contained in Maternity Dataset 1

Worksheet Name	Data Source	Data Field
NMDS (calendar year)	NMDS	Encrypted NHI
	NMDS	Date Event Ended
	NMDS	ICD-10-AM Code*
	NMDS	Diagnosis Related Group codes*
Prescription Data (calendar year)	Pharmaceutical Collection	Number of Prescriptions
	Pharmaceutical Collection	Encrypted NHI
	Pharmaceutical Collection	Dates Isotretinoin Dispensed
	Pharmaceutical Collection	Chemical Name
Demographic Data (calendar year)	PHO Enrolment Collection	Encrypted NHI
	PHO Enrolment Collection	Ethnic Group
	PHO Enrolment Collection	Age in Years
	PHO Enrolment Collection	DHB Name
	PHO Enrolment Collection	Deprivation Quintile

*Prior to 2012 NMDS data used Diagnosis Related Group codes and from 2012 the ICD-10-AM code was used.

Sorting the data by NHI codes allowed the following details to be analysed:

1) All maternity outcomes that occurred for each woman who had an isotretinoin prescription in the previous 12 months and when each maternity event ended.

2) The date of all the isotretinoin dispensings for each NHI code in each calendar year between April 2009 and the end of 2014.

The matched data over time provided a summary of each woman's journey with regard to isotretinoin prescriptions and subsequent maternity outcomes. The maternity codes were then grouped into categories of medical TOPs and live births.

3. Maternity Dataset 2

A second Maternity Dataset was obtained because prescriber type was not present in Maternity Dataset 1 and the isotretinoin dispensing date in each 12 month period before and after 1 March 2009 was required to fully address the research questions. This was obtained in Maternity Dataset 2 which contained the dates of isotretinoin dispensings for women having maternity outcomes within 15 months of any isotretinoin dispensing (the maximum period that could be accessed) and is shown in Table 6.

Table 6: Data Source and Data Fields contained in Maternity Dataset 2

Data Source	Data Field
PHO Enrolment Collection	Encrypted NHI
PHO Enrolment Collection	Age at dispensing
PHO Enrolment Collection	Ethnic Group
PHO Enrolment Collection	DHB Name
PHO Enrolment Collection	Deprivation Quintile
Pharmaceutical Collection	Encrypted NHI
Pharmaceutical Collection	Date Dispensed
Pharmaceutical Collection	Prescriber Specialty
BPAC	Decision Support Date
NMDS	Date Maternity Event Ended
NMDS	Days between Dispensing and Maternity Event
NMDS	ICD-10-AM Code*
NMDS	Diagnosis Related Group Codes*
NMDS	Clinical Code Chapter
NMDS	Clinical Code Description

*Prior to 2012 NMDS data used Diagnosis Related Group codes and from 2012 the ICD-10-AM code was used.

This allowed the number of days between maternity outcomes and the last isotretinoin dispensing to be calculated. If the maternity outcome was a TOP women who had been dispensed isotretinoin within six months of the TOP were identified. Where the time between isotretinoin and TOP was 6-8 months the days' supply of isotretinoin was also obtained as longer treatment periods may have meant these prescriptions were also linked (see linking databases in Section 2.4). The analytic approach to matching isotretinoin prescription and maternity event data is described in Appendix A.

3.3 Decision Support Data

The BPAC Decision Support tool includes a consent form from the GP confirming that patients whose care is guided by the tool understand that aggregated, non-identifiable information from this form may be used for population based health research as shown in Figure 6.

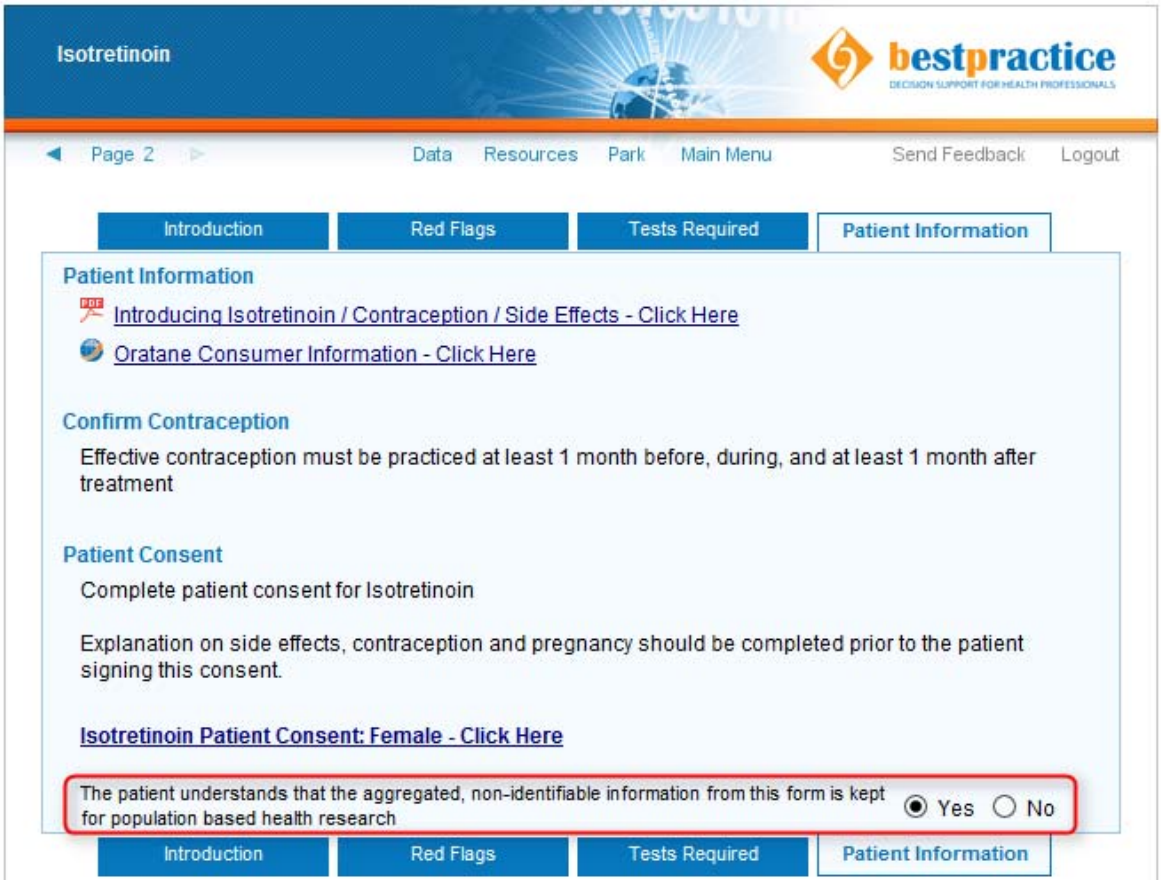


Figure 6: Confirmation patient understands use of these data for research

If the 'No' box was ticked at this stage of the module, a pop-up window appeared as shown in Figure 7. The clinician could still access the resources in the module and

continue the patient's care in the usual way, but would exit the module before any information was written to the patient record or the database used for this research.

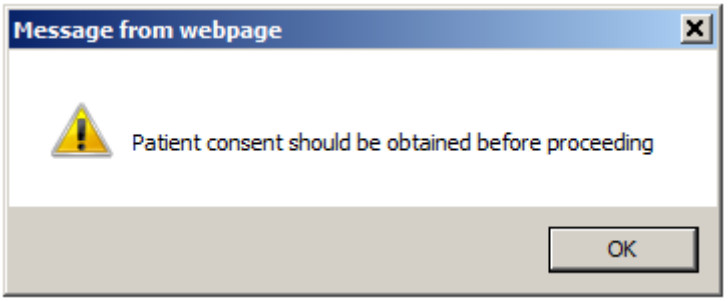


Figure 7: Pop-up window to prevent data being kept if patient does not agree to non-identifiable information being used for health research.

If permission was granted by the patient and recorded by the clinician in this way, the extraction of the Isotretinoin Decision Support module usage data was considered to have been given. The NHI codes in the decision support data are unencrypted and were never available for this research. Instead, the NHI codes were sent directly to the Ministry of Health for encryption using the same process as used for NHI encryption of other data from the Ministry of Health Collections. This enabled NHI codes of patients for whom the decision support module was accessed, and the date(s) it was used, to be matched with the data from Pharmaceutical and NMDS Collections.

Whereas many other decision support tools ensure guideline adherence for clinicians, the BPAC Isotretinoin Decision Support tool involves a patient consent form and patient information leaflets in an easily accessible form to print and personally discuss with the patient. Where patient compliance with recommendations around contraception and pregnancy-prevention is so essential to successful management of teratogenic risk, the module provides opportunities to enhance these processes during the consultation.

3.3.1 Cleaning Decision Support Data

The decision support usage data were called 'Decision Support Usage Dataset' shown in Table 7 and were supplied with the last dispensing date for each NHI code for the time period 1 January 2007 to 30 June 2015. This meant it was not possible to restrict the dataset to the study period of 1 March 2007 to 1 March 2015 only as dispensings other than the patient's last one were not available for each NHI code.

4. Decision Support Usage Dataset

The data source and data fields in the Decision Support Usage Dataset are shown in Table 7.

Table 7: Data Source and Data Fields contained in Decision Support Dataset

Data Source	Data Field
Pharmaceutical Collection	Encrypted NHI
Pharmaceutical Collection	Last Dispensing Date
PHO Enrolment Collection	Sex Code
PHO Enrolment Collection	Ethnic Code
PHO Enrolment Collection	Age at Dispensing
PHO Enrolment Collection	Deprivation Quintile
BPAC Decision Support Usage Data	Encrypted NHI (if Decision Support was used)
BPAC Decision Support Usage Data	Decision Support Date
NMDS	Date Event Ended
NMDS	ICD-10-AM Code*
NMDS	Diagnosis Related Group Codes*

*Prior to 2012 NMDS data used Diagnosis Related Group codes and from 2012 the ICD-10-AM code was used.

The data were filtered to find the total number of patients who had decision support used for their care over the study period. It was not possible to determine the total number of times the decision support module was used before an isotretinoin prescription because this dataset contained only the last dispensing date during the larger timeframe, including a few months either side of the study period.

The number of TOPs or exposed live births where decision support was ever used prior to the related dispensing could be divided by the total number of females whose prescriber ever accessed decision support to give a crude TOP rate and potentially exposed birth rate for women where decision support had ever been used. This was then compared to the same rate in all females accessing isotretinoin and in females who did not ever have the decision support module used for them. As the numbers involved were very small, individual analysis of the timing behind the decision support use in these

women was then done to determine which women actually had the decision support tool used for the related prescription before their TOP or exposed birth.

Linking Databases

This section will describe how the information from the various datasets was linked to analyse the circumstances around the isotretinoin dispensing, use of decision support and adverse maternity outcomes. Specific examples to illustrate the processes involved are included in Appendix B.

3.3.2 Decision Support and Maternity Data matching

The consistent Ministry of Health encryption process allowed the BPAC Decision Support data to be linked to the encrypted NHI codes of the NMDS, PHO Enrolment and Pharmaceutical Collections. The data were obtained with decision support dates detailed and the days between the isotretinoin prescription and the maternity event were calculated to create an additional field.

Once these databases were linked, the following outcomes were obtained:

- TOPs between 183–213 days for prescriptions of 31-60 days' supply
- TOPs between 214–243 days for prescriptions > 60 days' supply
- Live births between 341–370 days for prescriptions for 31-60 days' supply
- Live births between 37-400 days for prescriptions > 60 days' supply.

The duplicate NHI codes from these two datasets for each year were then investigated. If the last dispensing before the maternity outcome was for >30 days' supply the maternity outcomes were considered as having occurred during the period related to isotretinoin use.

3.3.2.1 Timing of Decision Support, Isotretinoin Prescription and Maternity Outcome

Prescriptions are funded for 90 days from when they are written so for decision support to have been used at the time of prescribing, it would typically have been used within 90 days of the first dispensing of that prescription. It is also possible within 90 days for

isotretinoin to have been freshly prescribed on a new prescription where decision support was not used.

To determine the number of women whose prescriber used decision support at the time of prescribing isotretinoin and then went on to have a TOP or exposed birth I calculated the time between decision support use and each dispensing date. This identified the patients whose primary care isotretinoin prescriber used the BPAC decision support module in the 90 days prior to the prescription dispensing. I checked all dispensing dates, and determined if subsequent dispensings over the following 90 days were from the original prescription's repeats, in which case decision support would not be used again, or if it was a new prescription where decision support could be used.

5. Decision Support and Maternity Data Matched

Table 8 shows the matched data from the Pharmaceutical Collection, PHO Enrolment Collection, Maternity Collection and the BPAC decision support usage data.

Table 8: Data Source and Data Fields contained in Decision Support and Maternity data matched

Data Source	Data Field
Pharmaceutical Collection	Encrypted NHI
Pharmaceutical Collection	Sex Code
Pharmaceutical Collection	Last dispensing Date
PHO Enrolment Collection	Ethnic Code
PHO Enrolment Collection	Age at Dispensing
PHO Enrolment Collection	Deprivation Quintile
BPAC Decision Support Usage Data	Encrypted NHI indicating Decision Support use
BPAC Decision Support Usage Data	Date of Decision Support use
NMDS	Date Maternity Event Ended
NMDS	ICD-10-AM Code*
NMDS	Diagnosis Related Group codes*

*Prior to 2012 NMDS data used Diagnosis Related Group codes and from 2012 the ICD-10-AM code was used.

The proportion of female patients whose care was guided by the BPAC Isotretinoin Decision Support module was found by filtering out males and removing duplicates to obtain the number of unique female NHI codes during the study period.

To ensure no duplication or other anomalies in the data and to fully understand the 'story' of each patient, the data was sorted by encrypted NHI code and each entry examined to fully determine each patient's encounters. Examples to illustrate the processes used are in Appendix B.

3.4 Ethical considerations

This research involved the analysis of data that was originally collected as part of a hospital discharge, PHO enrolment, isotretinoin dispensing or use of a decision support tool to enhance patient care. However the information was never personally identifiable and the identity of the prescribers and patients in this study was hidden from the principal researcher and supervisors at all times.

In collecting information for the NMDS, Pharmaceutical and PHO Enrolment Collection, the Ministry of Health is required to ensure the release of information recognises any legislation related to the privacy of health information, in particular the Privacy Act 1993 and the Health Information Privacy Code 1994[117]. In addition to this assurance, the BPAC Isotretinoin Decision Support tool specifically prompted the clinician to ask the patient if they consented to the use of the aggregated, non-identifiable information from the form being kept for population based health research.

If such consent was not granted, the patient's care was not affected in any way and the clinician was still able to access the same support and resources through the tool. However, in this case, the information was not recorded in the BPAC database nor was the module used to document the consultation in the patient record. In this case the prescribing clinician would record the consultation using their usual manual processes. Where consent was granted and recorded at the time of using the module, it was considered ethically sound to use the non-identifiable data in this research.

Ethical approval for this research was sought and granted from the University of Otago Human Ethics committee (Appendix C). A category B application was made as this project used encrypted NHI codes and de-identified data. Maori consultation was undertaken with the Ngai Tahu Research Consultation Committee (Appendix D). Jenny

McElroy is a current employee of BPAC CS LP but had no access to identifiable data at any time.

3.5 Chapter Summary

This chapter has described the design of the study and how the matching of the relevant data sources allowed appropriate analysis to answer the research questions.

4 Results

This chapter will describe the results of analysis of the isotretinoin usage, maternity outcome and decision support datasets.

4.1 Funded Isotretinoin Prescription Data

Descriptive analysis of the people who received isotretinoin prescriptions for the study period 1 March 2007 – 1 March 2015 was made based on patient age, gender, ethnicity and deprivation level.

Descriptive analysis of prescriber-type for the study period 1 March 2009 – 1 March 2015 was made. Prior to 1 March 2009 isotretinoin was funded only when prescribed by dermatologists so no analysis was done for the prescriber-type from 1 March 2007 to 1 March 2009.

4.1.1 Isotretinoin Access

During the study period a total of 53,863 patients were dispensed 211,374 prescriptions for funded isotretinoin. On average these patients had 3.96 prescriptions each and 7.56 isotretinoin dispensings. Isotretinoin is available in 10mg and 20mg capsule formulations only so to achieve a dose of 30mg, 50mg 70mg (etc) two prescriptions are required – one for 10mg capsules and one for 20mg capsules. The effect of this is that a count of the number of prescriptions for isotretinoin does not directly relate to the number of times isotretinoin is dispensed to unique patients.

Frequent dispensing of pharmaceuticals is permitted in New Zealand where dispensings are for less than a month's supply however the overall impact of these is small. For example in the year ending 28 February 2015 only 708 of the 54,688 dispensings were for 10 days' supply or less meaning patients with repeated frequent dispensings of <10 days' supply made up around 1.3% of dispensings in that year.

During the study period there were 26,388 prescriptions and 48,141 dispensings to patients with no NHI code. This constitutes 12.5% of the patients over the entire study period. However the impact of this diminished over the course of the study period: unidentified patients (no NHI code) contributed 18.8% of all funded dispensings in the first year data was available from 1 March 2007 to 29 February 2008. By the final year of the study period there were 890 unidentified dispensings or just 1.6%.

The number of patients accessing isotretinoin treatment increased steadily over the period. In the first year, 8,481 patients were dispensed isotretinoin and in the final year this number had increased to 13,846 patients, a 63.3% increase as shown in Figure 8.

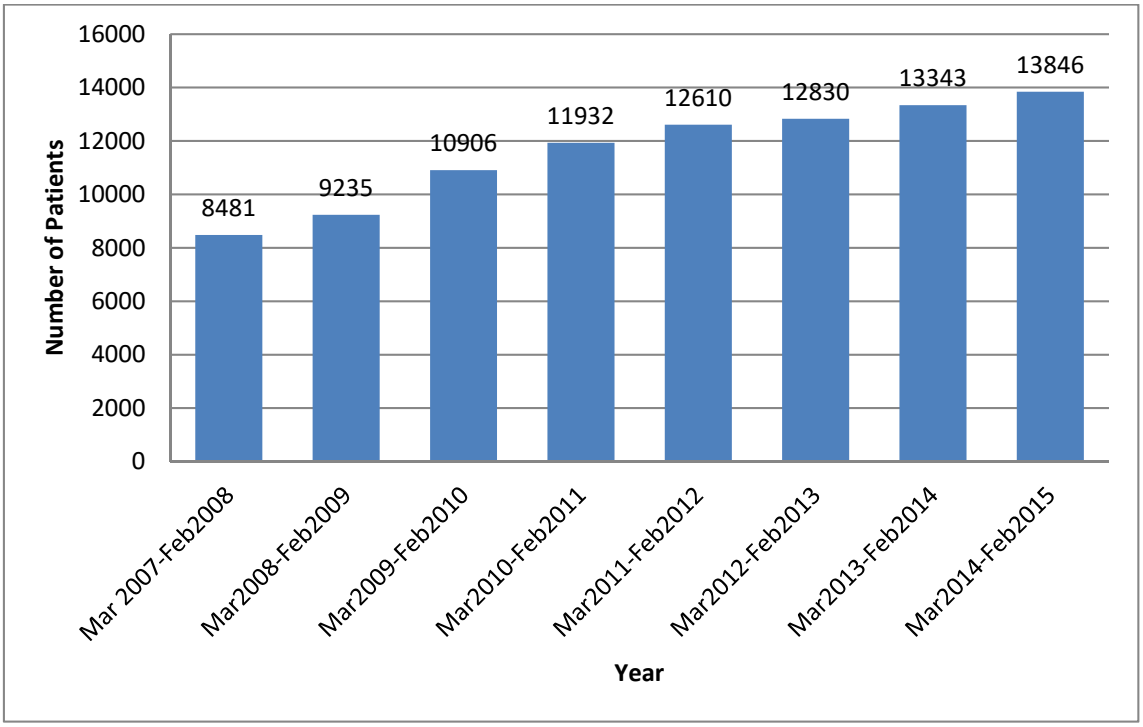


Figure 8: Number of Patients Dispensed Isotretinoin Annually

While there were already increasing numbers of patients accessing isotretinoin each year prior to the funding change in 2009, the annual increase doubled during the year following the change. This annual increase in patient numbers returned the following year to an increase similar to the year prior to the change as shown in Table 9.

Table 9: Percent Annual Increase in number of patients dispensed isotretinoin

Year	Annual increase %
Year 1	8.9
Year 2	18.1
Year 3	9.4
Year 4	5.7
Year 5	1.7
Year 6	4.0
Year 7	3.8

The number of patients accessing isotretinoin in New Zealand continues to increase each year, although this rate of increase dropped steadily in the three years after the year of the change in funding.

This section has shown access to isotretinoin increased over the study period with the largest annual increase in patients accessing isotretinoin being in the year following the funding change.

4.1.2 Isotretinoin use by age

Between March 2007 and February 2015, the most common patient ages at the time of isotretinoin being dispensed were 16 and 17 years as shown in Figure 9. The median age for isotretinoin to be dispensed was 19 years.

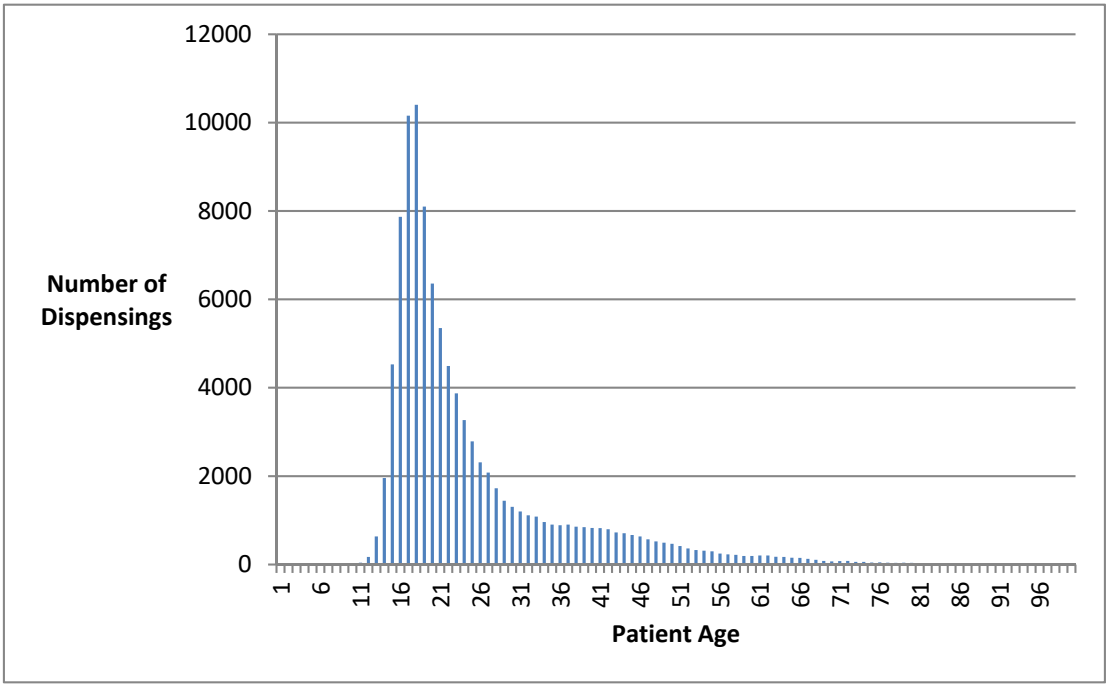


Figure 9: Patient age at Isotretinoin dispensing

People aged 10-30 years made up nearly 80% of patients who were dispensed isotretinoin although another 10% of prescriptions were for people aged 30-40 years.

4.1.3 Isotretinoin usage by Gender

Prior to the funding change on 1 March 2009 (Year 1 and Year 2 of the study period), 57% of patients accessing isotretinoin in New Zealand were female and 43% were male as shown in Table 10.

Table 10: Proportion of patients dispensed isotretinoin annually by gender

	Females %	Males %	Total
Year 1	57	43	8,481
Year 2	57	43	9,235
Year 3	56	44	10,906
Year 4	55	45	11,932
Year 5	56	44	12,610
Year 6	56	44	12,830
Year 7	56	44	13,343
Year 8	56	44	13,846

There were no significant changes to the proportions of people accessing isotretinoin by gender following the funding change in March 2009 as shown in Figure 10.

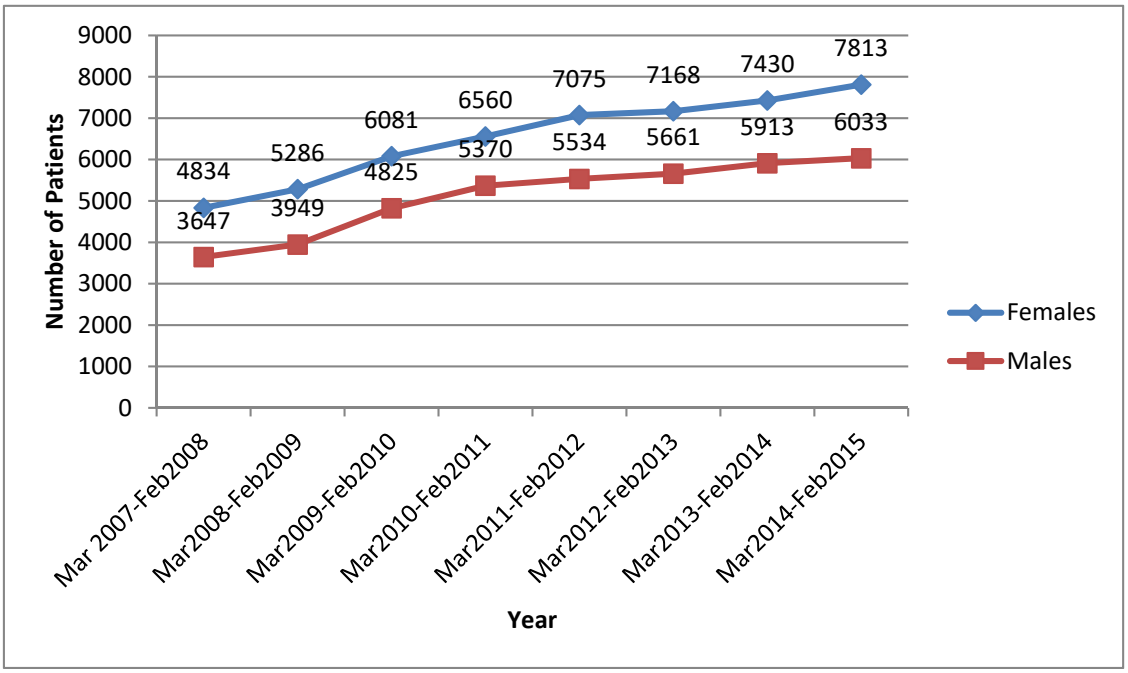


Figure 10: Gender of Patients Dispensed Isotretinoin

4.1.4 Isotretinoin Use by Age and Gender

The median ten year age band for males to access isotretinoin was 10-19 years and for females was 20-29 years both for the two year period prior to 1 March 2009 and in the six year period following 1 March 2009. In males, prior to the funding change on 1 March 2009, the 10-19 year age group was the most common age to use isotretinoin and this did not change following the change in funded access. Prior to 1 March 2009 the

most common age for females was 10-19 years and this showed a rapid decline in 20-29 year old females as shown in Figure 11. Following the change in isotretinoin funding there was an increase in the number of females who were dispensed isotretinoin in the age groups >20 years.

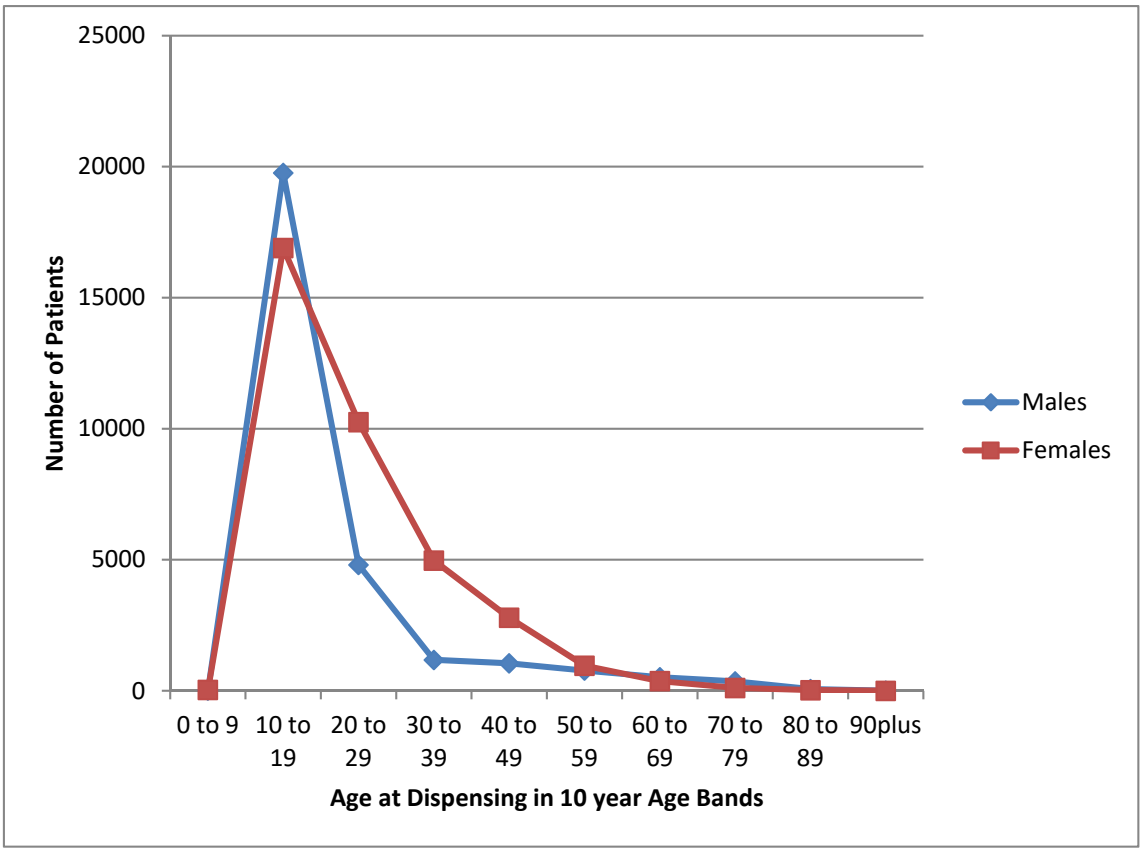


Figure 11: Age of Patients dispensed Isotretinoin from Mar 2007-Feb 2009 by gender

Following the change in funded access to isotretinoin after 1 March 2009, the number of females accessing isotretinoin aged 20-29 did not decline as sharply from the peak use by 10-19 year old females as it had done when accessing funded isotretinoin required a dermatologist visit. Prior to March 2009, the number of female patients using isotretinoin in their 20s was 60% of the number who used it in their teenage years. From 2009 to 2015 the number of females using isotretinoin in their twenties was 79% of the number using it in their teens. This demonstrates that females have been more likely to be prescribed or continue with isotretinoin after the age of 20 since 1 March 2009.

4.1.5 Isotretinoin usage by Ethnicity

There were changes in the proportional ethnicities of the people dispensed isotretinoin from March 2007 to February 2015 as shown in Figure 12. The absolute numbers of

European people accessing isotretinoin increased more than any other ethnic group and reflects the overall increase in isotretinoin use for this period of around 50%.

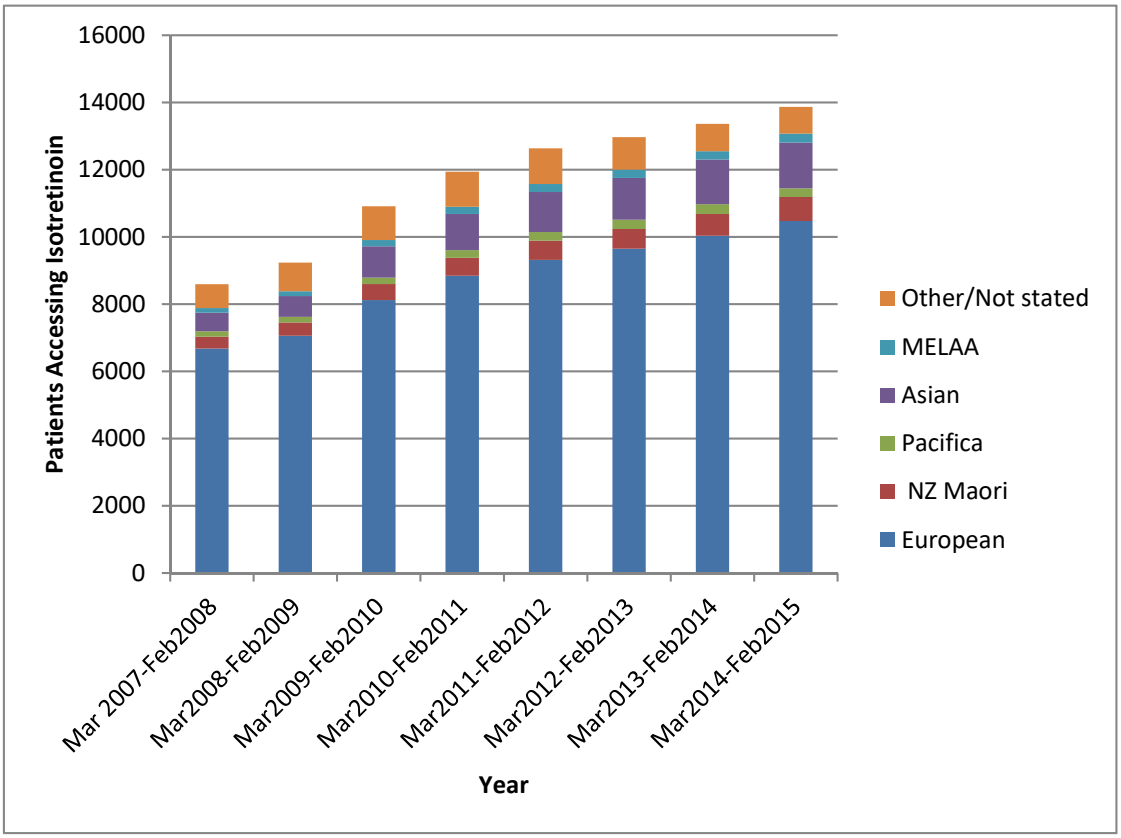


Figure 12: Ethnicity of People Dispensed Isotretinoin

However, the other ethnic groups of Maori, Pacific, Asian and MELAA have shown larger proportional increases as shown in Table 11.

Table 11: Change in Ethnicity of Isotretinoin Patients since Funding Change

	European	Maori	Pasifika	Asian	MELAA*	Other/Not Stated	Total
Mar2008-Feb2009	7,059	397	164	619	145	853	9,237
Mar2014-Mar2015	10,471	715	258	1,362	265	796	13,867
% Increase	48%	80%	57%	120%	83%	-7%	50%

*MELAA = Middle Eastern/Latin American/African

The most notable proportional increase in use of isotretinoin during the study period is the Asian group who now access isotretinoin in numbers proportional to their total

numbers in the New Zealand PHO population. Despite the proportional increases in Maori of 80% and Pacific peoples of 57% taking isotretinoin from 2009 to 2014, they were still under represented compared to their numbers in the New Zealand population as shown in Table 12.

Table 12: 2014-2015 Ethnic proportion compared to proportion of Isotretinoin Users

2014 - 2015	European	Maori	Pasifika	Asian	MELAA*	Other/Not Stated
% of Isotretinoin users	75.5	5.2	1.9	9.8	1.2	5.7
% of PHO population	65.2	14.6	7.3	10	1.9	1.6

*MELAA = Middle Eastern/Latin American/African

4.1.6 Isotretinoin Usage by Deprivation Level

The number of patients accessing isotretinoin in the most deprived groups, deprivation quintile 1 and 2, showed a 74% increase from 1 March 2009 to 1 March 2015. This was the largest increase with deprivation quintile 3 increasing 68% and deprivation quintile 2 increasing 55%. The 50% increase in the least deprived group reflected the overall increase in numbers accessing isotretinoin in total. However as previous inequities in access to isotretinoin had been identified for the most deprived groups, the largest absolute increase in numbers was in the least deprived people as shown in Figure 13.

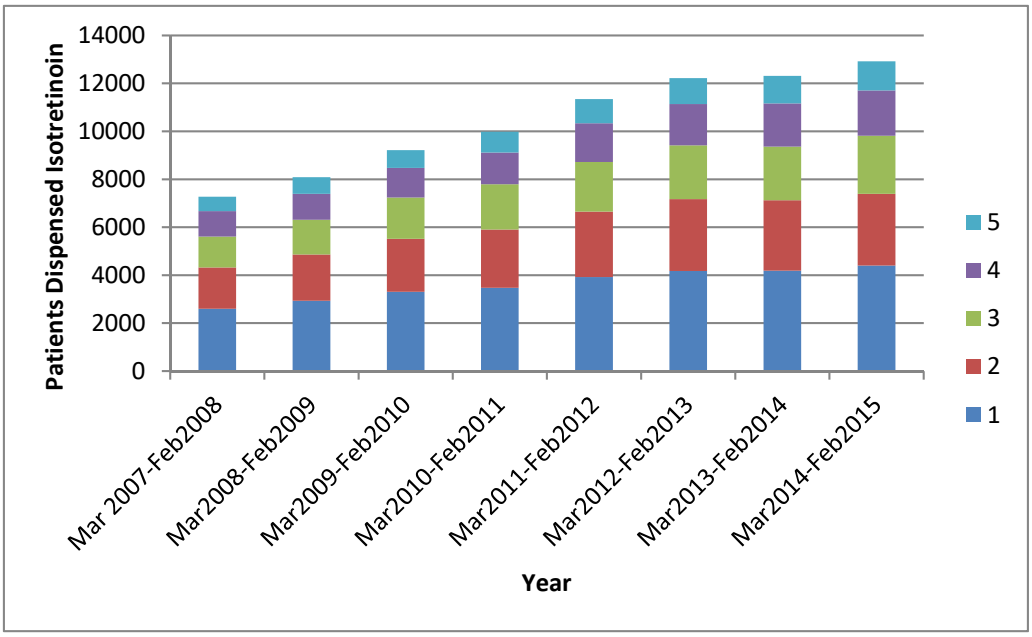


Figure 13: Deprivation Quintile of Patients Dispensed Isotretinoin

4.1.7 Days' supply per dispensing

Throughout the study period the most commonly prescribed length of supply for isotretinoin was 30 days. This is consistent with PHARMAC's policy for isotretinoin to be dispensed in monthly allocations unless prescribers endorse prescriptions as a 'certified exemption' or patients sign for an Access Exemption due to travel, relocation, physical mobility or transport issues.[123]

There was a slight increase between the year ending March 2008 and the year ending March 2015 in the number of prescriptions dispensed for over 60 days' supply from 1.6% to 2.8% of all prescriptions respectively. This is illustrated for females in Figure 14 and for males in Figure 15.

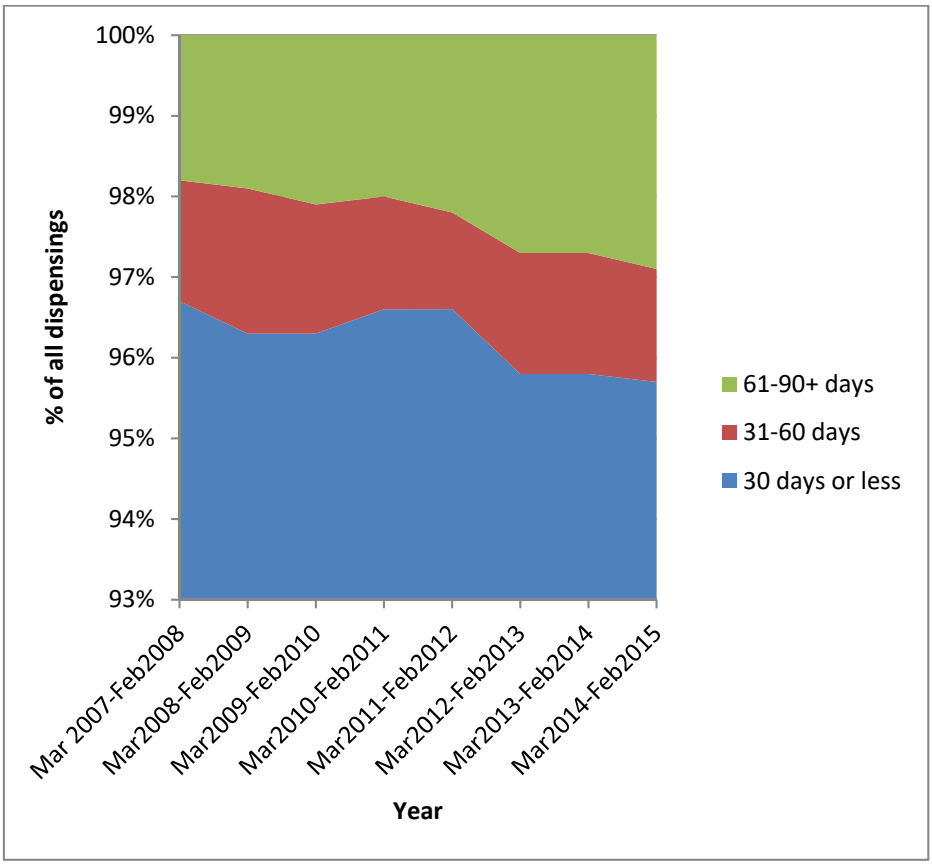


Figure 14: Days' Supply per Female Dispensing

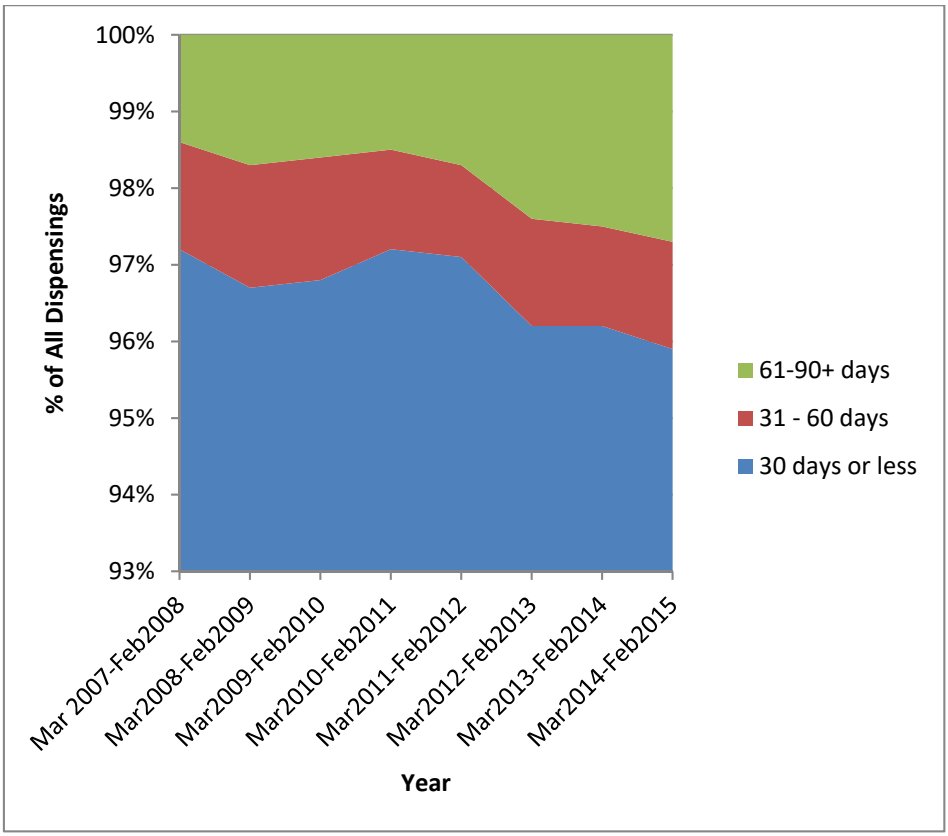


Figure 15: Days' supply per Male Dispensing

The significance of this change for females is the potential lack of contact with a health professional during the 2 months after dispensing to re-enforce the message about contraception being required during treatment and to discontinue treatment if pregnant. Females consistently collected more supplies of greater than 30 days than males although the difference was small.

4.1.8 Isotretinoin Usage by Prescriber-Type

The number of patients accessing isotretinoin from dermatologists has declined steadily since funded access was widened to include other prescribers with a Special Authority. In the year ending 28 February 2015 GPs prescribed isotretinoin to 50% more patients than dermatologists. There has been a sustained trend of fewer dermatology prescribers and more GP prescribers since the funding change on 1 March 2009.

Although application for Special Authority to prescribe isotretinoin must be made by a dermatologist, GP or nurse practitioner, other prescribers continue to prescribe funded isotretinoin with a Special Authority. Although dermatologists and GPs are by far the most common prescribers of isotretinoin, there are still around 1,000 patients having

isotretinoin prescribed by other prescribers each year. The number of Unknown prescriber type has decreased over the study period as shown in Figure 16.

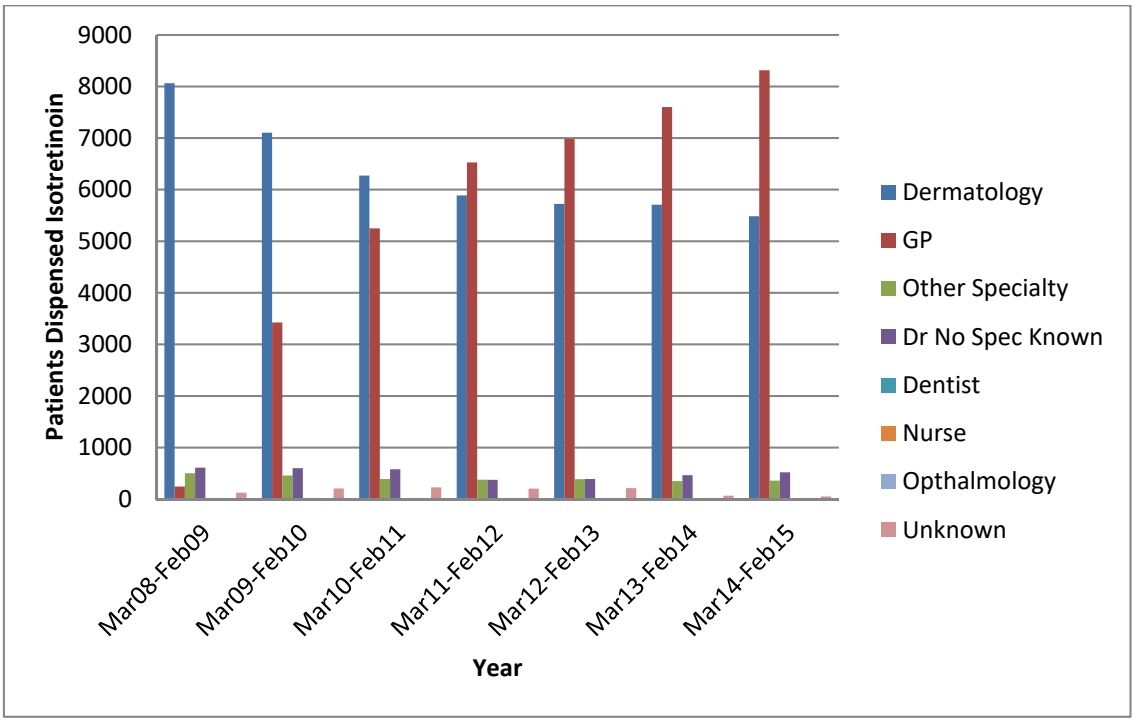


Figure 16: Patients Dispensed Isotretinoin by Prescriber Type

In the twelve months prior to 1 March 2009, 8,062 patients were dispensed isotretinoin that had been prescribed by a dermatologist and the number of people prescribed isotretinoin by a dermatologist decreased by around 1,000 patients in the first year following the funding change. This first year after GPs were able to prescribe funded isotretinoin saw 3,425 patients access the medication this way and this number increased by 53% in the following year and 24% in the year to 1 March 2012 as shown in Table 13. The increase continued in the following three years so that by the year ending 1 March 2015 more patients were prescribed isotretinoin by their GP than had obtained it from a dermatologist prior to the funding change.

Table 13: Percent Change in Patients Dispensed Isotretinoin by Prescriber Type

	Mar 08 - Feb 09	Mar 09 - Feb 10	Mar 10 - Feb 11	Mar 11 - Feb 12	Mar 12 - Feb 13	Mar 13 - Feb 14	Mar 14 - Feb 15
Dermatology	8,062	7,104	6,273	5,887	5,723	5,709	5,486
% change		-12%	-12%	-6%	-3%	-	-4%
GP	244	3,425	5,250	6,526	6,984	7,602	8,315

% change			+53%	+24%	+7%	+9%	+9%

4.2 Use of BPAC Decision Support Module

This section will describe the use of the BPAC Decision Support Isotretinoin module in New Zealand for the period when usage data was available between 1 January 2007 and 30 June 2015.

4.2.1 Use of BPAC Decision Support Module by Gender

From 1 January 2007 to 30 June 2015 there were 63,054 isotretinoin dispensings for 56,919 patients (unique NHI codes). Of these patients, 31,261 were females and 25,655 were males, with 3 of unknown gender. There were 2,932 females and 2,549 males whose prescriber used decision support to guide their isotretinoin prescribing (9.4% and 9.9% of female and male patients respectively).

These numerical observations do not directly provide information about the impact on maternity outcomes of decision support use unless the timing of this decision support use is considered in relation to a maternity outcome. For example, a GP using decision support after an isotretinoin-related maternity event has not helped to avoid that event.

4.3 TOPs in Women Dispensed Isotretinoin

This section will describe the TOPs in women dispensed isotretinoin during the study period from 1 March 2007 to 28 February 2015. This crude data will be converted to a TOP rate per 1,000 females accessing isotretinoin and compared to the TOP rate for all females aged 15–44 in New Zealand. The TOP rate for all females in New Zealand is not available, but less than four percent of prescriptions for isotretinoin during the study period were to females aged under 10 years or over 50 years. No females aged under 10 years or over 50 years who were dispensed isotretinoin during the study period had a subsequent TOP.

4.3.1 Isotretinoin prescriptions and TOP

Across all study years there were 161 TOPs that could be matched with an isotretinoin dispensing in the preceding six months (seven months if 60 days' supply of isotretinoin and eight months if 90 days' supply isotretinoin). Figure 17 shows the distribution by study year.

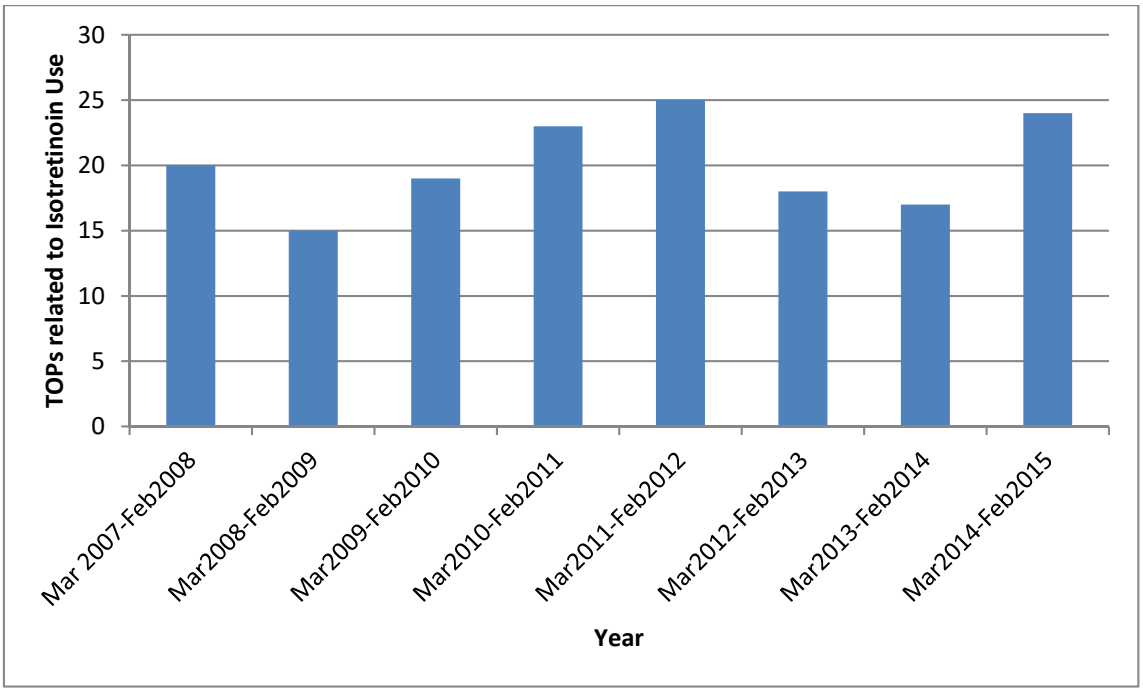


Figure 17: TOPs in Women Dispensed Isotretinoin

4.3.2 Comparative TOP Rate for Isotretinoin Users

By dividing the number of TOPs in women dispensed isotretinoin in Figure 17 by the total number of females who accessed isotretinoin in each year as in Figure 10, a crude TOP rate per 1,000 females can be calculated. The crude TOP rate for all females aged 15–44 years in New Zealand over the study period declined from 19.7 to 14.2.[124] For women who had a prescription for isotretinoin in the preceding six months this rate dropped from 4.6 to 3.3 as shown in Figure 18.

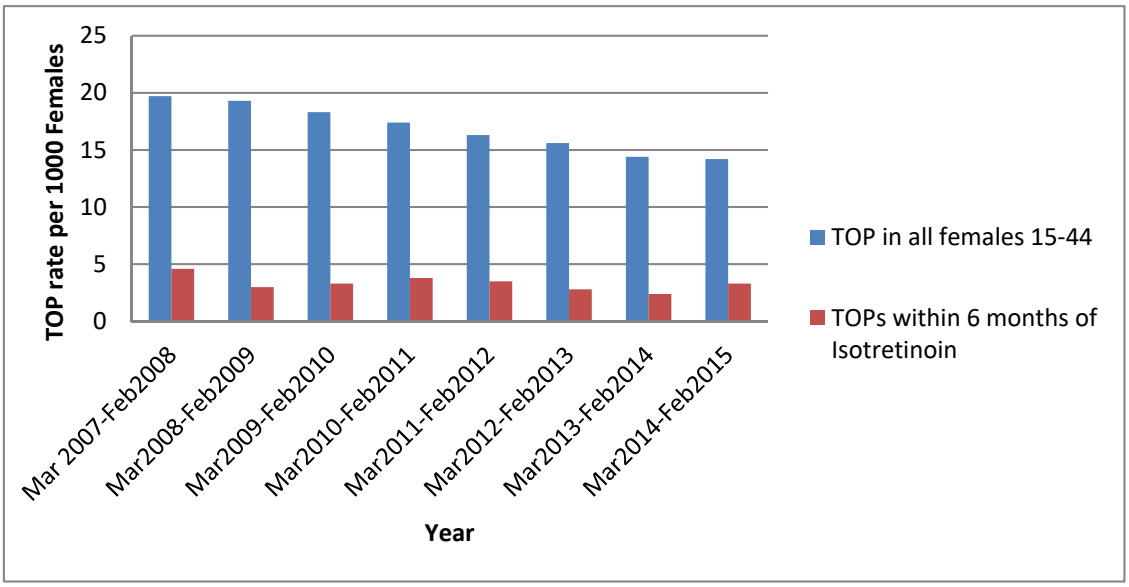


Figure 18: TOP Rate per 1,000 Females

4.3.3 TOP Rates by Prescriber Type

The absolute number and rate of TOPs per 1,000 females dispensed isotretinoin for each prescriber-type are shown in Figures 19 and 20.

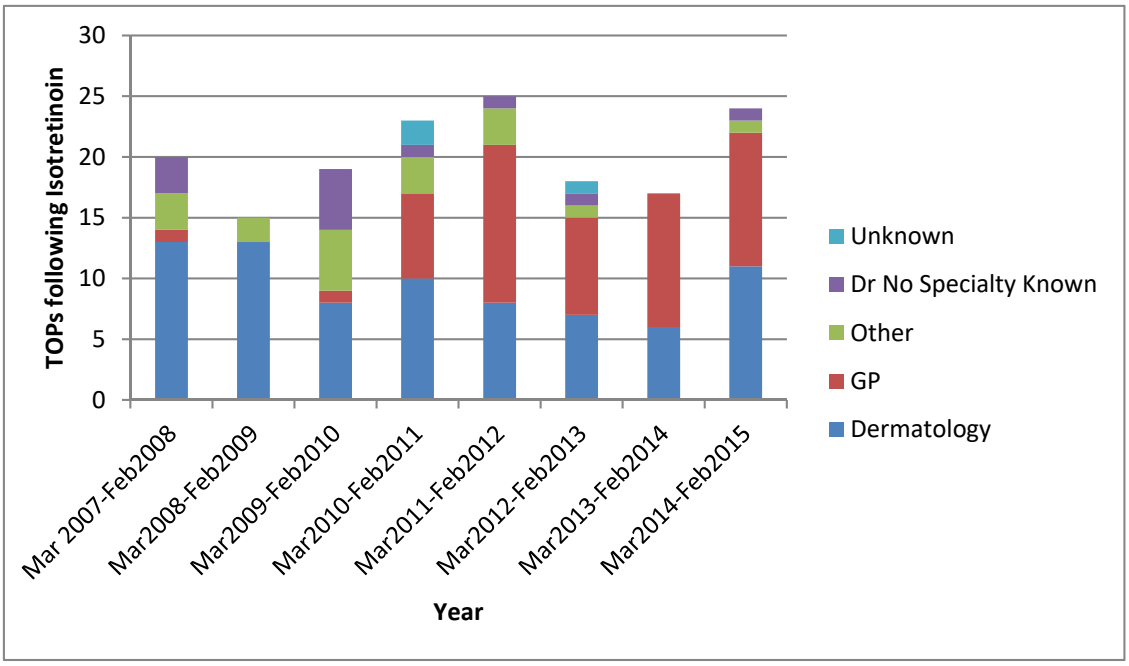


Figure 19: TOP by Prescriber Type

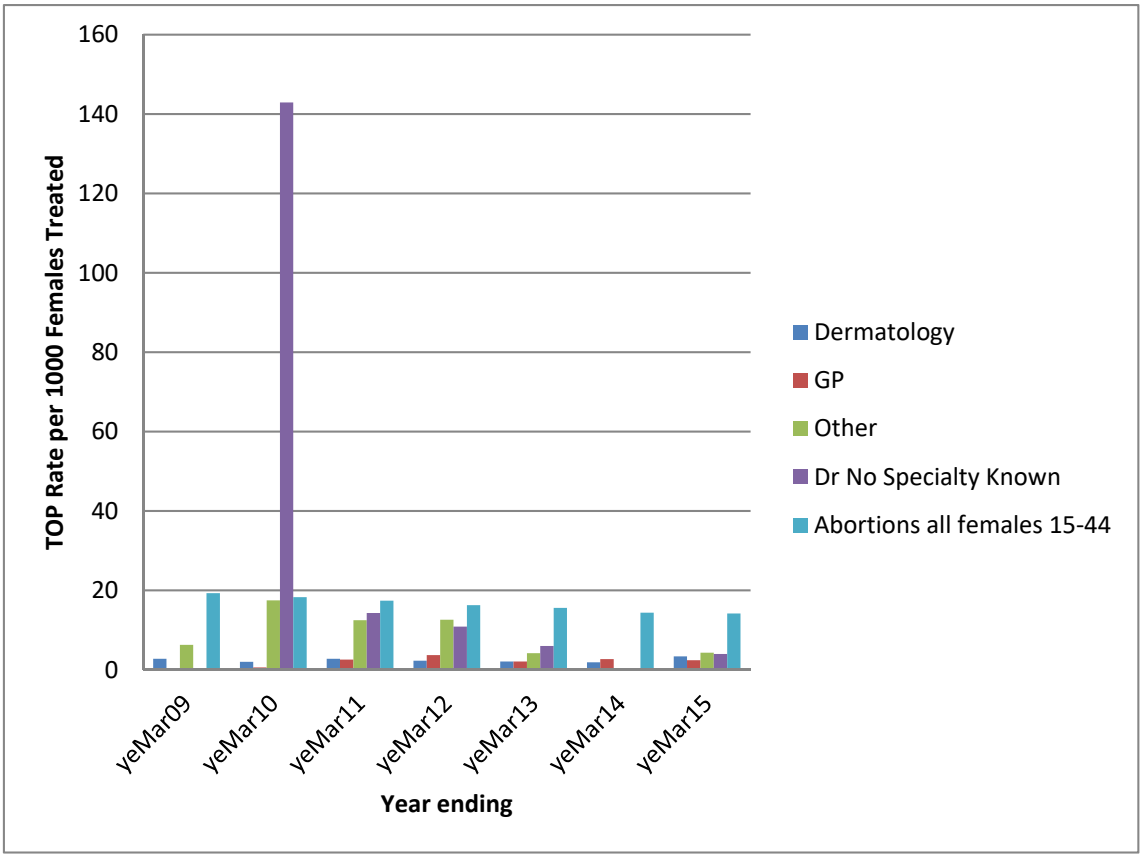


Figure 20: TOP Rate per 1,000 Females Treated by Prescriber Type

The TOP rate for Dermatology prescribers of isotretinoin has ranged between 1.9 and 3.4 per 1,000 females treated since the year ending March 2009. For GP prescribers since the funding change this rate has been marginally higher between 2.1 and 3.7. This compares to a crude TOP rate for all females aged 15–44 that has dropped from 19.3 to 14.2 over this time.

In the year ending February 2010 there were 5 TOPs to women dispensed isotretinoin during the related period for both 'Other Prescribers' and for 'Dr No Specialty Known'. In this year 'Other Prescribers' wrote isotretinoin prescriptions for 285 female but only 35 patients were recorded as 'Dr No Specialty Known'. This equates to a TOP rate per 1,000 females treated of 17.5 for 'Other prescribers' and 142.9 for 'Dr No Specialty Known' reflecting a relatively high number of TOPs for a small number of females treated . These rates subsequently dropped to below the crude rate for all females although remained higher than for GPs and Dermatology in the following three years. There were no events attributed to these prescribers in the year ending March 2014. The rate in the year ending 2015 was slightly higher than GPs and dermatologists, although more in line with their prescribing than it had been previously.

4.4 Live Births Exposed to Isotretinoin

This section will describe the number of live births that occurred to females who had isotretinoin prescriptions dispensed within the guideline period.

4.4.1 Isotretinoin prescriptions and Exposed Live Births

Live births where the infant was potentially exposed to isotretinoin during pregnancy have been identified and shown by prescriber type in Figure 21. This study suggests up to 16 births per year in New Zealand may be exposed to isotretinoin in-utero. Dermatologist, GP and other prescribers' prescriptions contribute to these exposures. Since 1 March 2011 GPs have prescribed isotretinoin for more patients each year than dermatologists and since this time there have also been more potentially exposed live births each year due to their prescriptions.

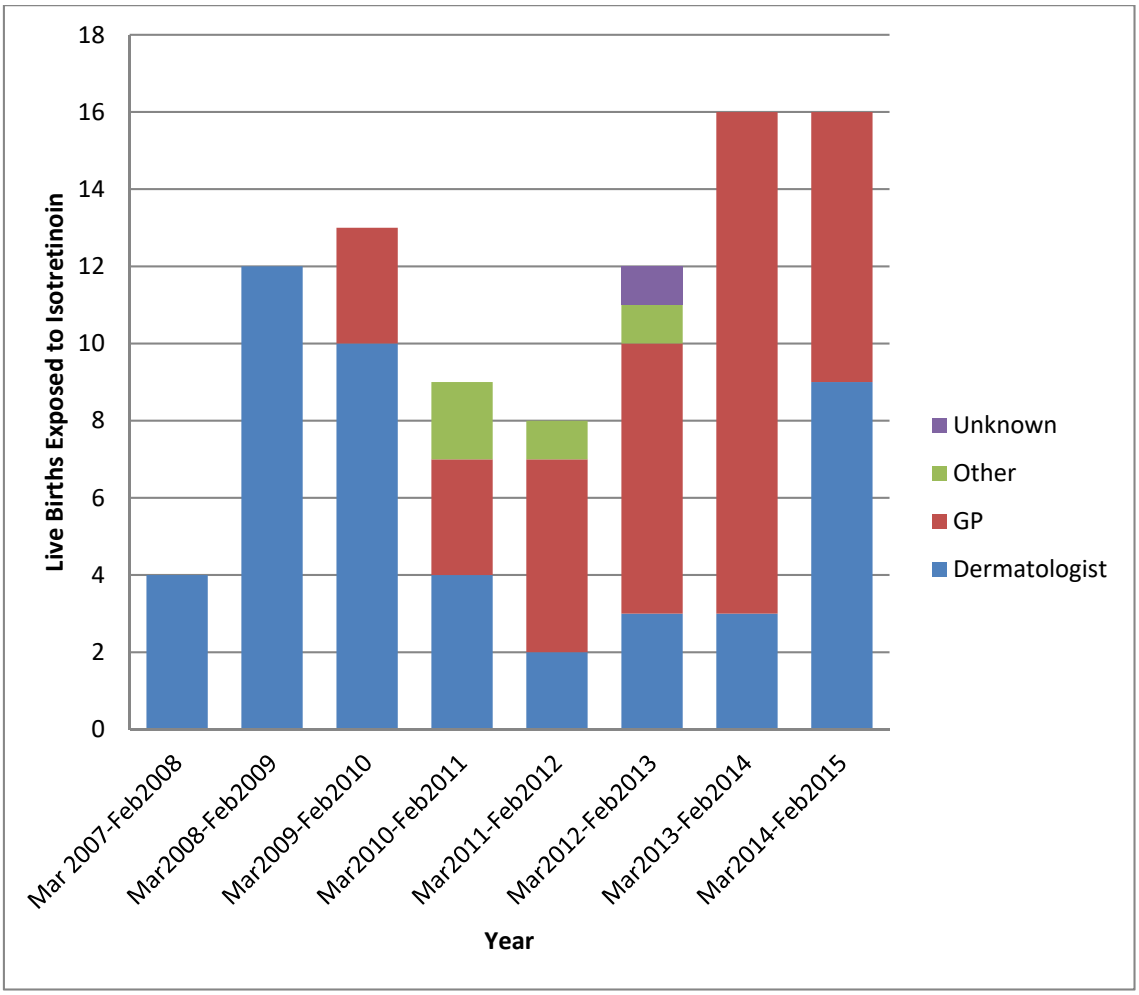


Figure 21: Live Births Exposed to Isotretinoin

NB: Two births following GP prescriptions in the year ending March 2013 occurred very closely to the guideline period of 400 days at 389 and 399 days following a prescription for isotretinoin. It is possible these women adhered to guidelines but infants were born slightly early however they have been included in these totals as they fit the guideline criteria.

Figure 22 shows the rate of exposed live births per 1,000 females treated for the different prescriber types illustrating lower rates for dermatologists and GPs than the 'Other' or 'Specialty Unknown' prescribers.

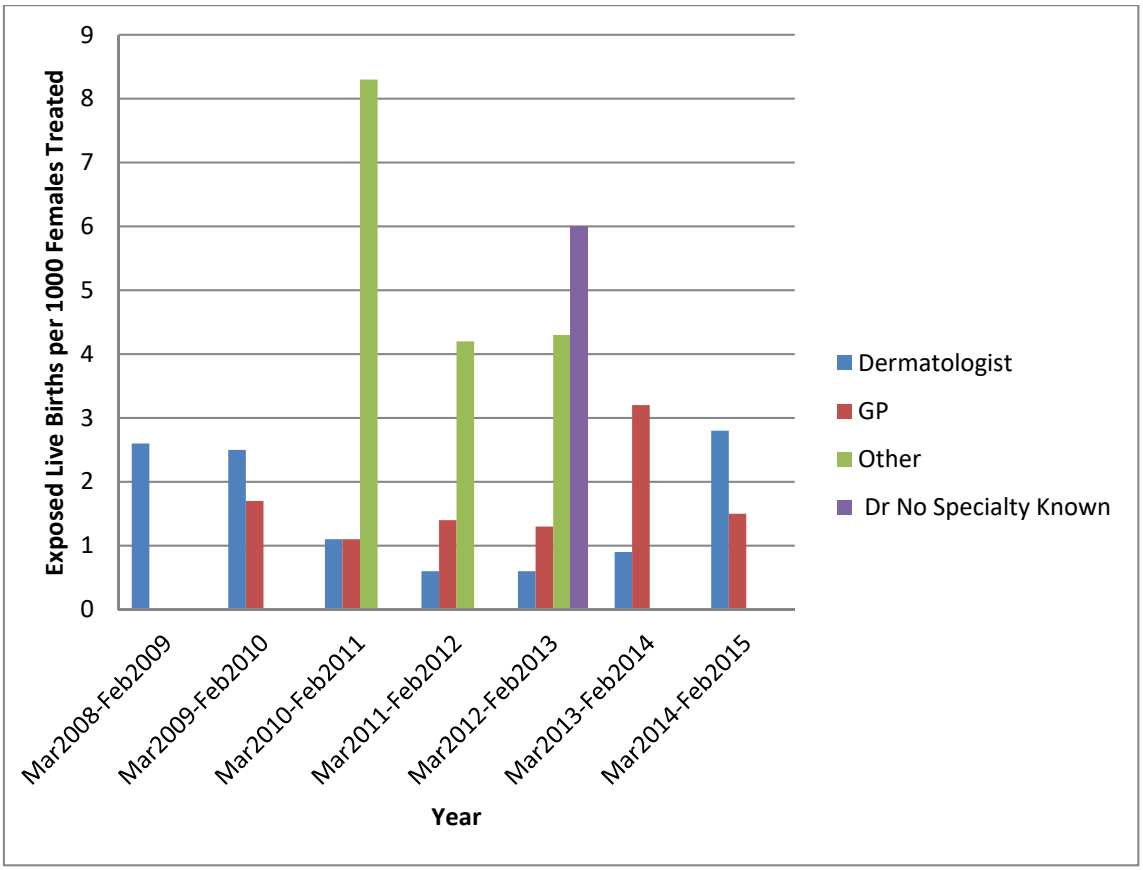


Figure 22: Rate of Exposed Live Births per 1000 Females Treated by Prescriber Type

4.5 Decision Support Data

This section will describe how many of the patients who had TOPs and potentially exposed live births following isotretinoin treatment had the BPAC Decision Support module used and the number of patients where it was used for the related prescription. The rate of these events per 1,000 women treated with isotretinoin will be calculated.

4.5.1 TOP rate for prescribers using Decision Support

There was one TOP during the linked period following isotretinoin dispensing when the prescriber used decision support for that isotretinoin prescription in the year ending March 2011 and there were two in each year ending March 2012 and 2014 as shown in Figure 23. There was one additional TOP in the year ended 1 March 2011 and another in the year ended 1 March 2015 where decision support had been used for this female previously but not for this prescription.

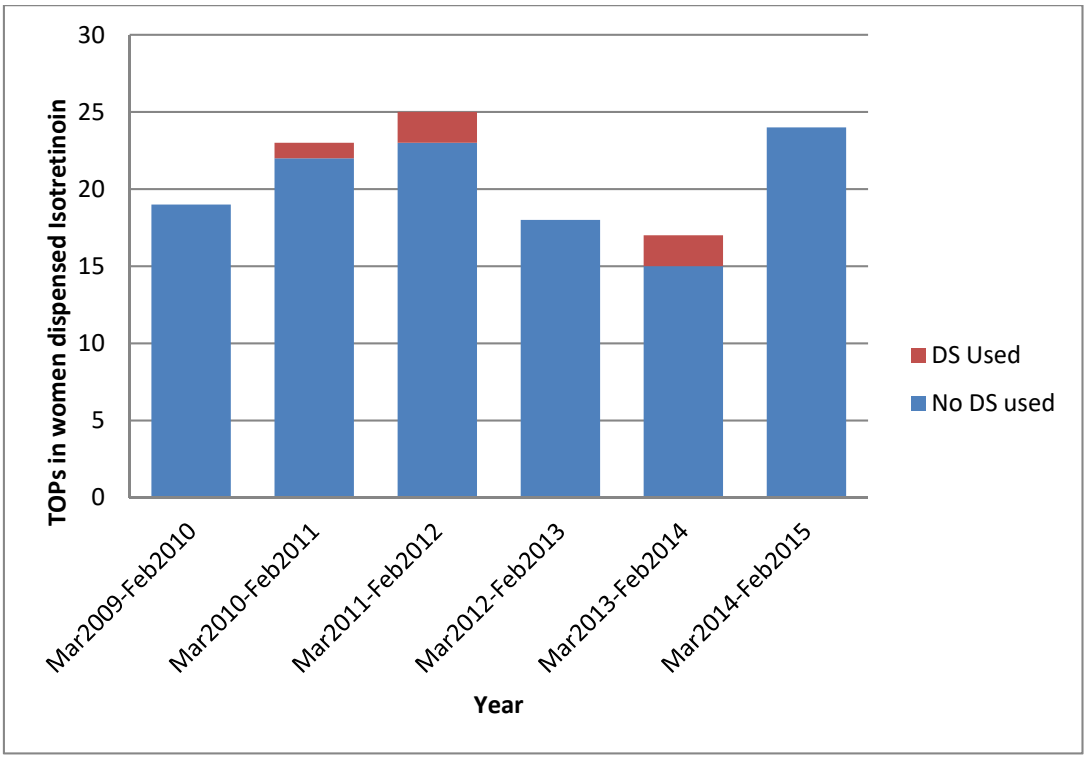


Figure 23: TOPs in women Dispensed Isotretinoin where Decision Support was used

The decision support module was used for 2,293 of the 21,499 females who had isotretinoin prescriptions between 1 March 2009 and 1 March 2015 which allowed a TOP rate per 1,000 females treated to be calculated for those women who had ever had decision support used to guide their prescribing as shown in Figure 24.

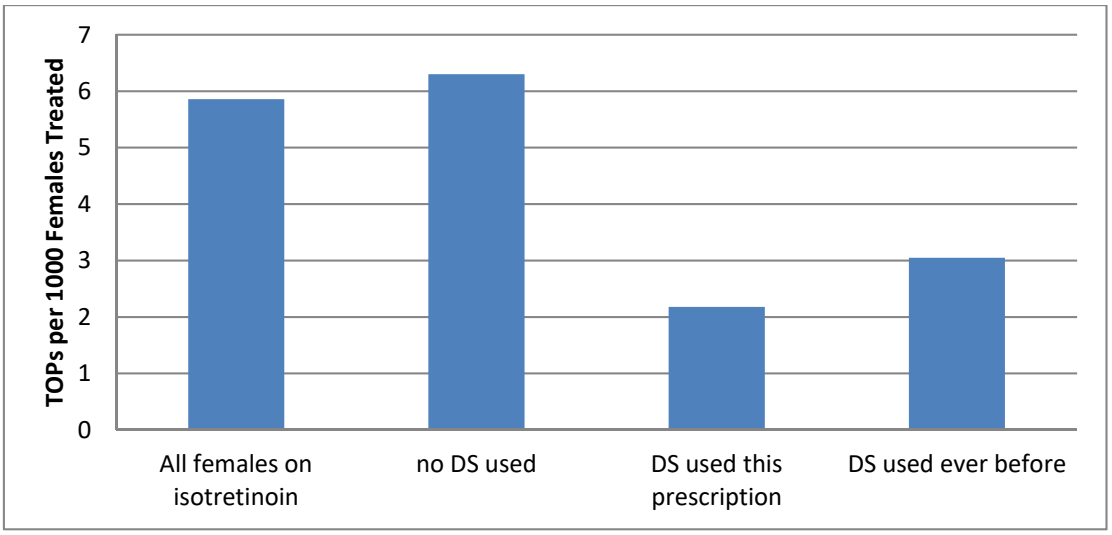


Figure 24: TOPs per 1,000 Females Treated

4.5.2 Exposed Live Birth Rate for Prescribers using Decision Support

Of the 71 potentially exposed births since the funding change on 1March 2009, there were two instances in the year ended 1 March 2014 and one in the year ended 1 March 2015 where the BPAC Decision Support tool was used prior to the linked isotretinoin prescription as shown in Figure 25. There was one additional potentially exposed birth in the year ended 1 March 2014 where decision support had been used for this female previously but not for this prescription.

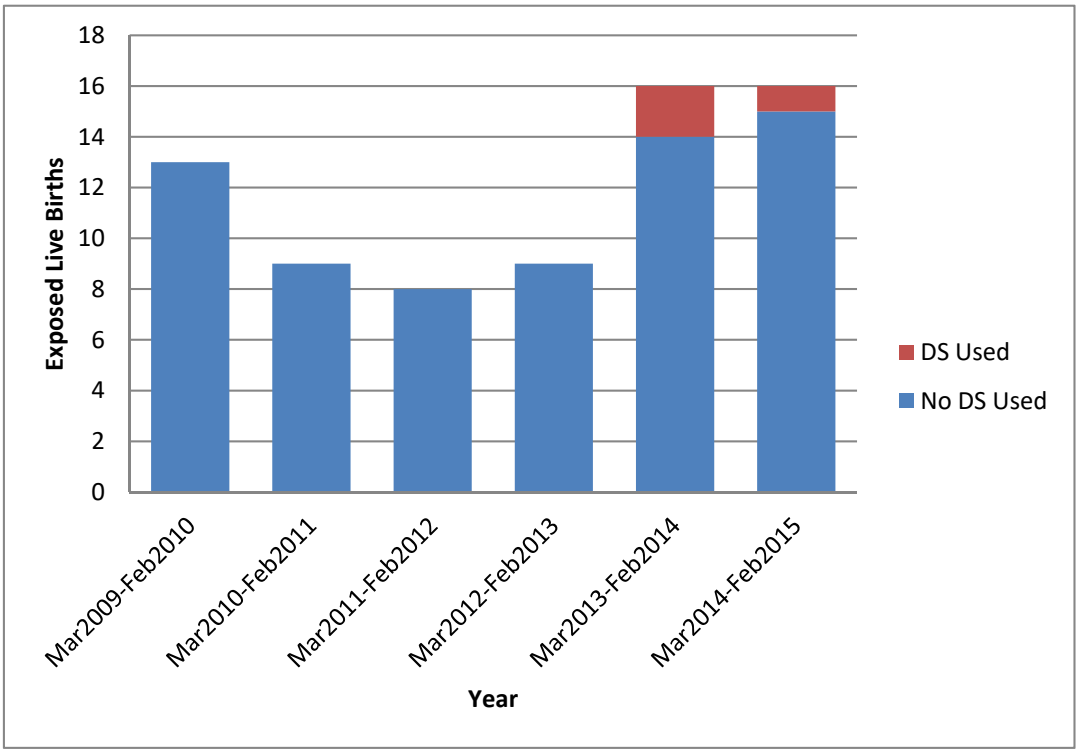


Figure 25: Potentially Exposed Live Births where Decision Support was used

Figure 26 shows the rate of potentially exposed live births per 1,000 females treated with isotretinoin for all females treated with isotretinoin and compares this to the rate where decision support was not used, where it has ever been used for that woman, and where it has been used for the prescription that resulted in an exposed live birth.

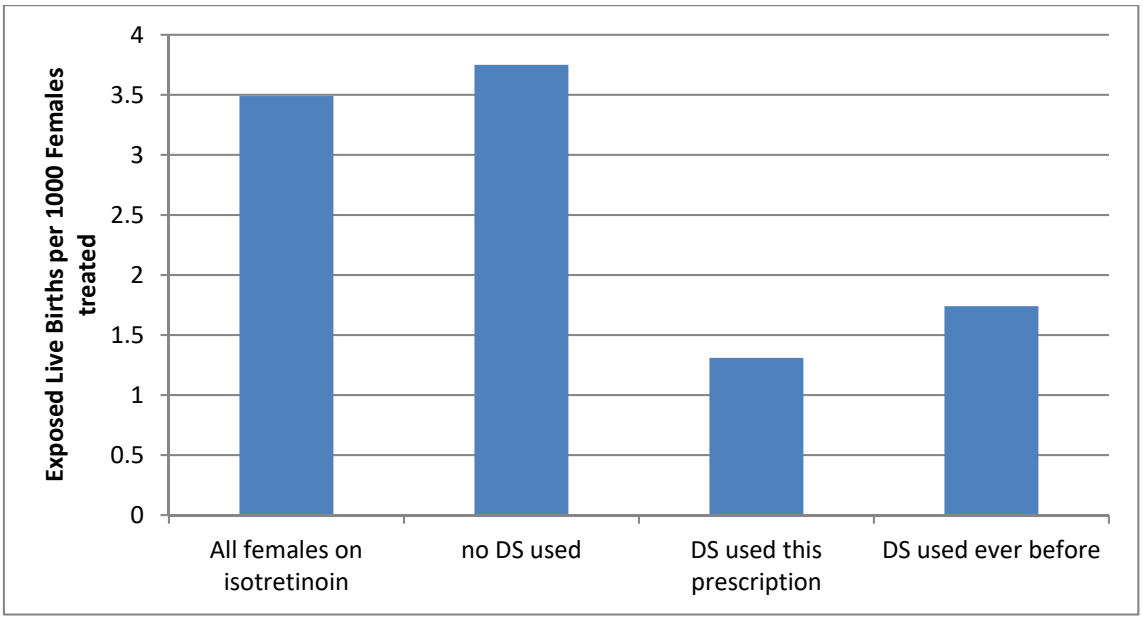


Figure 26: Potentially Exposed Live Births per 1,000 Females Treated

4.6 Chapter Summary

This chapter has described the results of the data analysis. The usage and maternity outcomes in women dispensed isotretinoin during the linked period were addressed. This was done by age, gender, ethnicity, deprivation level and prescriber-type. The links between maternity outcomes and the use of decision support were also described. A discussion of these results is in the following chapter.

5 Discussion and Recommendations

This chapter will review the results of this study in light of the currently known information about isotretinoin access and TOPs and exposed live births occurring in women who have taken isotretinoin during the linked period. The recommendations and areas for future research that have come out of the study are presented. The limitations and strengths of the study are also discussed.

5.1 Main Results

The number of patients accessing isotretinoin continued to increase year on year from 1 March 2007 to 1 March 2015 although the immediate increase in isotretinoin use after the funding change rapidly dropped off to rates similar to before the change. This suggests more restrained increase in isotretinoin use after that time and reflects patterns previously identified in other moves to improve healthcare access.[125]

It is not clear if this increased use reflected an increasing awareness and therefore demand for oral acne treatment or was meeting a previously unmet need. Isotretinoin has remained the only agent of its type for the treatment of severe acne, and moderate acne after antibiotics and where topical agents have failed. No new alternative agents have been introduced to the market over the study period that might have impacted the number of patients accessing isotretinoin.

This study has confirmed the differences found elsewhere in the age distribution of males and females seeking medical attention for acne also occur with isotretinoin in the New Zealand context.[89] Teenage males are the group who access isotretinoin the most by age and gender. Since isotretinoin also became funded through GPs and nurse practitioners, proportionally more females have continued to use isotretinoin after the age of 20 than they had previously. This could potentially reflect that the additional GP prescribers were less reluctant to prescribe isotretinoin to sexually active females over 20, or could reflect the widening use of isotretinoin in milder acne which females of this age are more likely to have (see 1.1.3.4 above). This is significant because females are more likely to be regularly sexually active in their 20's than they are between the ages of 10 and 19. Increased access and use of isotretinoin by females of child-bearing age who are sexually active must address the teratogenic risks of this agent to ensure its safe use and avoidable pregnancies.

Although starting from an under-represented proportion of the population, ethnicities other than European have made proportionally larger increases in the numbers accessing isotretinoin since the funding change on 1 March 2009. Although the largest absolute increase in isotretinoin users are European, this is proportional to the overall increase in its use during the study period. By contrast the proportion of Asians has increased 120% compared to the proportion of Asian isotretinoin users prior to the funding change. This might have had more significant implications on the TOP rate of isotretinoin users and be an ongoing issue for the future if the TOP rate for Asians which was previously the highest ethnicity, had not declined to be similar to that of Maori and Pacific women since 2012.[124]

The percent of people dispensed isotretinoin who identify as Maori and MELAA has increased 80% over the years since the funding change while the overall increase in access has been 50%. Pacific people had the smallest proportional increase in isotretinoin use other than Europeans at 57%. The change in funded isotretinoin has helped address inequities for access to isotretinoin for non-European ethnicities in New Zealand.

While no New Zealand data exists to confirm the prevalence of acne in Maori and Pacific people, these increases may have gone some way to addressing the previously recognised inequities of isotretinoin access to these ethnicities. However the largest increase in the absolute number of people accessing isotretinoin in any one ethnicity was seen in Europeans. This may reflect a greater perception of 'problem acne' in fairer skins where the redness from inflammation is more noticeable, cultural differences in the importance of acne and fewer barriers to accessing health services in Europeans.

The most deprived people have made proportionally larger increases in numbers accessing isotretinoin since the funding change suggesting the change has helped address inequities for access to isotretinoin for the most deprived groups in New Zealand. The trend for females to collect more than 30 days' supply of isotretinoin at once should be discouraged in sexually active females of child bearing age unless a negative pregnancy test is required monthly.

The introduction of GP prescribing of funded isotretinoin in New Zealand has made this treatment for severe acne available to more patients than were accessing it previously through dermatologists. In New Zealand GP and dermatologists are now the dominant prescribers of isotretinoin.

For the purposes of this study, a TOP within 6 months of an isotretinoin prescription or an isotretinoin-exposed live birth are both considered to be adverse health outcomes. TOPs continue to occur in New Zealand during the period of time following isotretinoin dispensing that suggests they may be related to isotretinoin use. The rate for these TOPs per 1,000 females is roughly 20% the TOP rate for all females aged 15-44 in New Zealand. While it would be ideal to avoid any unplanned pregnancy during the use of a teratogenic acne treatment, the lower rate compared to all females indicates caution is being used in prescribing isotretinoin in New Zealand. Any steps to further consistently reduce this rate, while maintaining access to a very effective treatment when it is needed, would contribute to even safer use of this teratogenic medicine.

The female patients of dermatologist and GP prescribers of isotretinoin demonstrate similar rates of TOP following isotretinoin dispensing. This was a surprise finding as GPs' experience of prescribing and discussing contraception with women had been considered as one reason their prescribing might result in even fewer pregnancies following isotretinoin dispensing than dermatologists. Perhaps this finding mirrors the previous finding in the US where GPs were shown to be the second most frequent providers of prevention and counselling categories including issues related to obstetrics and gynaecology when compared to other office-based medical specialties.[126]

The total number of TOPs following isotretinoin dispensing identified in this study were significantly lower than the previous study for the year ending June 2008 by Moodie et al.[40] I am unable to examine the raw data from the previous work and cross-check it against my own so cannot validate their methods. In particular it would be valuable to confirm each of the 39 TOPs reported by their analysis was a separate maternity event rather than being the number of isotretinoin prescriptions where a TOP occurred within the following six months.

In the first few years when isotretinoin could be prescribed by clinicians who were not dermatologists, the women whose prescriptions were written by 'other prescribers' and 'doctors whose specialty is unknown' went on to have a TOP following isotretinoin more often than women whose isotretinoin-prescriber was a GP or dermatologist. The number of prescriptions from these other or prescribers of unknown specialty was small suggesting prescribers who were familiar with the use of isotretinoin may have offered better support and guidelines to women about the need to use two forms of

contraception if they are sexually active and that they should not become pregnant while they are undergoing treatment and for 30 days after.

While isotretinoin is prescribed to sexually active women of child-bearing age there is a risk of babies being exposed to this teratogen in-utero. Minimising this risk should remain a key component of appropriate prescribing in our communities. This study demonstrated certain prescriber-types potentially expose a disproportionate number of babies to isotretinoin in-utero suggesting regulators should carefully examine how these prescribers can be supported to remove or minimise this risk.

Although the total numbers are small, women who have had the BPAC isotretinoin decision support module used are less likely to have a TOP within six months of an isotretinoin prescription and are less likely to have a baby delivered that has potentially been exposed to isotretinoin in utero. This outcome is even more pronounced if the BPAC module was used for the related isotretinoin prescription.

As there were 162 TOPs within six months of an isotretinoin prescription in the six years following the funding change on 1 March 2009 and 9.4% of females had the BPAC isotretinoin decision support used for them, it might be expected there would be 16 TOPs where the module was used. There were five TOPs where decision support had been used which suggests 11 terminations of pregnancy may have been avoided by the use of the module during this time. Alternately, if every prescriber had used the BPAC isotretinoin decision support tool to guide his prescribing to females, the number of TOPs following isotretinoin could have been reduced from 162 to 50.

There were 69 potentially exposed births in the six years following the funding change and if 9.4% of females had decision support used, seven births could be expected where the module was used. There were three births where decision support was used for the isotretinoin prescription involved which suggests exposure to isotretinoin in utero may have been avoided for four children. If all prescribers had used the BPAC decision support tool, the number of babies exposed to isotretinoin could possibly have been reduced from 69 to less than 30.

This study has demonstrated improved maternity outcomes where the BPAC isotretinoin decision support module is used to guide prescribers. However the use of any guideline support tool that is optional may reflect the more cautious, guideline driven practice of the prescribers who chose to use it. Improved access to isotretinoin

decision support for all prescribers and steps to increase its use every time isotretinoin is prescribed may help reduce adverse health outcomes for women taking this teratogenic medicine and their babies.

5.2 Recommendations

With the availability of such comprehensive and valuable data about outcomes from the New Zealand health system the challenge is to convert this knowledge into wisdom that transforms the future.[127] Funding for isotretinoin through GPs has increased its availability to lower socio-economic groups and ethnicities that have previously faced inequitable access barriers. This knowledge could be applied to other pharmaceuticals where current funding is only through specialist-only prescribing and alternative treatments do not exist. Where there is a likely benefit for more patients to have improved health from increased access to these restricted agents, but little potential for harm, the widening of funded access to include vocationally registered GPs and nurse practitioners should be explored.

Prescribers other than GPs and dermatologists do not prescribe isotretinoin often but when they do, the maternity outcomes for their female patients are poorer. Isotretinoin may be used more safely when funded access is restricted to dermatology and vocationally registered GP and nurse practitioner prescriptions only.

The BPAC Isotretinoin Decision Support tool has helped facilitate safer prescribing of isotretinoin. This module was developed in 2009 and has had consistent use, but for less than 10% of all isotretinoin patients since that time. Investment in updating the module to a format reflecting other decision support tools commonly used in 2016 that are more readily adopted by clinicians has the potential to lead to safer maternity outcomes for female patients and avoid babies being exposed to this teratogen.

The widespread use of decision support tools that engage female patients and prescribers in understanding when a medicine may cause birth defects, and that promotes the ongoing commitment to two forms of contraception during treatment, has the potential to lead to safer prescribing of all teratogenic agents. Optimal benefit is most likely to be achieved if this support is implemented every time a teratogenic agent is prescribed, and re-enforced with subsequent pharmacy dispensings.

5.3 Areas for Future Research

- The isotretinoin maternity dataset obtained for this study contains the ICD-10-AM codes O00 to O03 which are ectopic pregnancies, hydatidiform moles, other abnormal products of conception and spontaneous abortions. Future analysis of this data is possible to determine the adverse maternity outcomes in New Zealand women taking isotretinoin for the 15 month period following oral treatment however this did not form part of the current study.

- The isotretinoin Usage dataset obtained for this study could also be analysed to understand changing doses and treatment periods over the study period. With the evidence for a cumulative dose regime having been challenged since isotretinoin was first registered in New Zealand, it would be valuable to quantify current prescribing patterns to identify if lower doses are being used for longer treatment periods. This analysis would inform future measures for understanding and managing adverse effects over extended time periods.

- Future qualitative research into the obstacles and enablers to accessing isotretinoin treatment and concurrent effective contraception across all ethnicities and deprivation levels is an important area for future research. This understanding would inform a review of the pathways to isotretinoin access with the goal of achieving equitable and safe access for this very effective agent.

- The isotretinoin maternity dataset contains information about the ages, ethnicities, District Health Boards (DHBs) and deprivation levels for the women who had TOPs or exposed live births following isotretinoin treatment. Further analysis of these demographics would identify areas with greater need for support in managing the teratogenicity of isotretinoin and ensure efforts to address these needs are directed appropriately.

- Currently no data is available about where patients get information on isotretinoin teratogenicity or the level of patient understanding of the issue. Qualitative research addressing what information patients want and how they would like to receive it would help ensure the most effective delivery so future harms can be minimised.

- The patterns of usage for the current BPAC decision support module by gender, ethnicity, deprivation level and DHB of clinician and patient may allow better

understanding of the barriers and facilitators to its use when prescribing isotretinoin. Currently there is no data available to clarify when prescribers use decision support and why they don't use it. Qualitative research to determine what prescribing support isotretinoin prescribers want and how it should integrate with current processes will also inform the development and implementation of the most effective prescriber support possible.

5.4 Strengths of this study

This is a population based study analysing all the New Zealand population data for eight years. The NHI code is the primary enabler to allow this matching of data from different sources. The ability to link data is particularly strong because of the existence and widespread use of the NHI code throughout the New Zealand health system. The observations made in this study illustrate the value of New Zealand data for the purpose of analysing links between healthcare and outcomes.

As well as the matching of data from a number of different sources, this study also included individual review on a case by case basis, driven by original research questions, to identify any anomalies and to verify the links. It is descriptive research but it is very comprehensive and replicable. It also meets many of the recommended goals of evaluation for risk-minimisation programmes in that it has been without extra burden on either healthcare professionals or patients and has used existing data sources to measure outcomes in a practical, feasible and easy to collect manner.[116]

The opportunity to analyse the impact on health outcomes of a change in funding for an established medication is rare. The opportunity to do so with such detail on a whole nation's data is even more so. As far as I have been able to ascertain there is no other published literature indicating a whole nation's isotretinoin dispensing data has ever been analysed and matched with TOP and maternity data in such careful detail to analyse the impact of a funding change. With varied global approaches to managing the teratogenic risk of isotretinoin, this study adds to the universal understanding of how prescriber type impacts these outcomes.

This study meets the recommended requirements of an evaluation method for a risk-minimisation measure in that it is tailored to specific safety concerns, the actual decision support tool used and the drug involved.[128] It is the first time the outcomes for female patients whose prescriber did not use an isotretinoin decision support tool to

guide their prescribing have been compared with the outcomes in patients whose prescribers did voluntarily use the tool.

The study illustrates the potential for decision support to successfully guide the prescribing of teratogenic agents without increasing barriers to access. As a minimum, the steps in the decision support module relating to female patients understanding this drug can cause birth defects, the need for contraception and the advice not to get pregnant for 30 days as minimum has clearly been shown. The outcomes of this study may encourage health planners to re-think regulation that allows prescribers who are not familiar with isotretinoin to prescribe it. This therefore becomes valuable to New Zealand health managers to inform future approaches to managing teratogenic agents.

In addition, with various approaches to prescribing isotretinoin and other teratogenic agents globally, this study demonstrates the relative impacts prescriber-type and the use of decision support can have on maternity outcomes. Other nations whose standard of clinical care is similar to the New Zealand situation may consider how this may be used to improve the outcomes in their context.

5.5 Limitations of this study

1. TOP statistics reported by Abortion Supervisory Committee include all legal induced TOPs in New Zealand but despite a recommendation that private TOP clinics include NHI codes in their reporting this has not occurred. In the most recently available data from 2014 there were 13,137 legal TOPs in New Zealand with 931 (7%) of these at the Auckland private clinic. These procedures are not included in the data from the NMDS which is for publicly funded services only and none of these 7% have NHI codes so cannot be linked to isotretinoin prescribing. Similarly for the last three years Tauranga Family Planning Clinic has been doing medical TOPs which do not require a hospital discharge so are not included in this sample.
2. Some of the women who chose to attend the private Auckland TOP clinic may have done so as they were ineligible for funded healthcare in New Zealand. These same women would not receive funded prescriptions for isotretinoin and therefore their prescriptions would also not form part of the Pharmaceutical Collection data. This means the true number of TOPs in New Zealand following isotretinoin use may be higher than the publicly funded figures represented in this study.

3. The number of unknown NHI codes limits the accuracy of this data as all demographics and any NMDS maternity event matches are lost for these dispensings. The number of these Null NHI code dispensings has decreased over the study period as shown in Figure 27 meaning maternity events following isotretinoin prescriptions will have been under reported in the earlier part of the study period. During the entire study period from 1 March 2007 to 28 February 2015 there were a total of 26,388 prescriptions and 48,141 dispensings where the NHI code was not available. This constitutes 12.5% of the patients over the entire study period.
   The impact of prescriptions with Null NHI codes diminished over the course of the study period with 33.4% of prescriptions having a Null NHI in the year ending 1 March 2009, 16.3% in the year ending March 2010 and 12.3% in the year ending March 2011. Since that time, the prescription data has contained less than 10% Null NHI codes.
   In the year ending 1 March 2009 the proportion of Null NHI codes was 33.4% of all dispensing data and, as this was nearly all dermatologists' prescribing, reflects the lack of NHI code use by these prescribers at the time. As GP prescribing of isotretinoin has increased, this proportion of unknown NHI codes has significantly decreased to be just 1.6% of all dispensings in the year ending 1 March 2015.

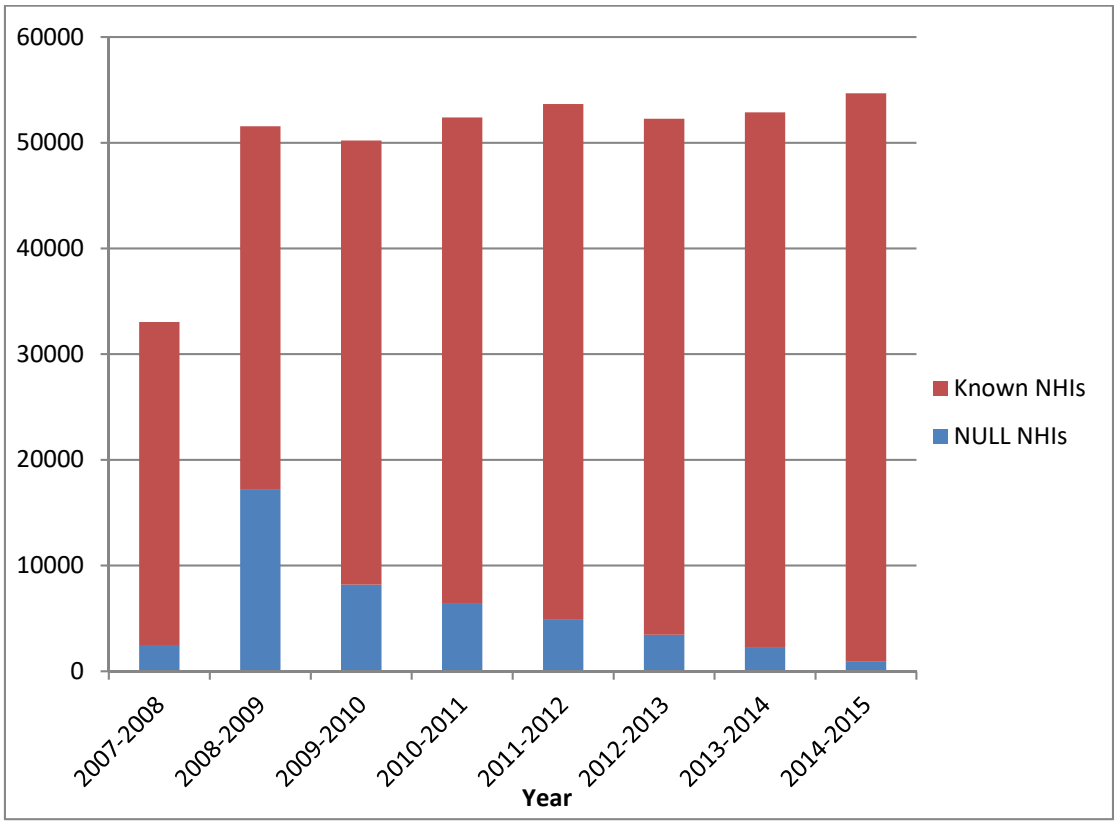


Figure 27: Isotretinoin Prescriptions with NULL NHI in Usage Dataset

4. It is realised that a number of pregnancies do not last 280 days and this may have meant this study over-estimated the potential exposure to isotretinoin during pregnancy. However, pre-term birth is considered an adverse pregnancy event in itself, some pregnancies go beyond term, and many patients miss days of medication after picking up prescriptions meaning they are still taking medication beyond the expected treatment period. Considering these possibilities, this study has implemented the stated time periods as there may be both under-estimates and over-estimates which could cancel each other out.

5.6 Chapter Summary

The study was concluded in this chapter with a discussion of the strengths and limitations of this research. The recommendations that were made after completion of this work and areas for future research have been discussed. This chapter concludes this study.

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Appendices:

Appendix A: Analytic approach to Ministry of Health isotretinoin prescribing and maternity data

The cleaned data from Maternity Dataset 2 was analysed as follows:

1. First I filtered out all maternity events using the 'days between' column where any maternity event was more than 183 days (i.e. 6 months) after an isotretinoin prescription.

2. This gave the NHI codes for women with maternity events within six months and I filtered out all events that were not TOPs. (The same process was used later to analyse the exposed pregnancies where I filtered to obtain the potentially exposed live births in the appropriate timeframes).

3. I copied this cohort to a new worksheet entitled 'TOP < 183 days' from where I could sort by dispensing date. This allowed all the TOPs from each 12 month period from 1 March 2007 to 1 March 2015 to be counted.

4. I also wanted to include any TOP events between 183 and 243 days where more than 30 days' supply of isotretinoin had been dispensed, to reflect the continued exposure from larger dispensing quantities. To do this I filtered the dataset in the same way to identify NHI codes where the days between isotretinoin dispensing and TOP were 183-243 days.

5. For each 12 month period ending 1 March, I matched this list of women with a TOP in 6-8 months against the women who had been dispensed more than 30 days' supply in each year. By matching duplicates, I found NHI codes appearing in both lists and checked if they had a TOP within 213 days with 31 - 60 days' supply or 243 days with 61 - 90 days' supply. This identified an additional 4 linked events for the entire study period that could be individually analysed.

Appendix B: Worked examples of data linking

Four examples are detailed below to illustrate the data linking processes that were used and different outcome scenarios:

1. *TOPs where Isotretinoin had been Dispensed*

Example 1: Data illustrating identification of a TOP where Isotretinoin had been Dispensed

eNHI	ETHNIC	dhb	DEP	dispense date	speciality	DS Date	date_event_ended	days between date dispensed and ho	diag1002	diag1003	diag1004	diag1005	Clini ca	Comments and story
788dN3bCvCw			4	24/11/2011	GP		8/02/2013	442						
788dN3bCvCw			4	19/12/2011	GP		8/02/2013	417						
788dN3bCvCw			4	17/01/2012	GP		8/02/2013	388						
788dN3bCvCw			4	26/07/2012	Dermatology		8/02/2013	197						
788dN3bCvCw			4	29/08/2012	Dermatology		8/02/2013	163	O049 from NMDS and rx matching dates					7 rx (last on 15/10/12) then TOP 3.5 months later on 8/2/13; then a second TOP 9 months later on 15/11/13 (no more iso during int
788dN3bCvCw			4	29/08/2012	Dermatology		15/11/2013	443	O049 Medical abortion from NMDS and rx matching dates					
788dN3bCvCw			4	30/09/2012	Dermatology		15/11/2013	411						
788dN3bCvCw			4	30/09/2012	Dermatology		1/12/2013	427	O034 from NMDS and rx matching dates					NB: Two isotretinoin-related TOPs + one TOP not related
788dN3bCvCw			4	30/09/2012	Dermatology		1/12/2013	427	O043 from NMDS and rx matching dates					
788dN3bCvCw			4	30/09/2012	Dermatology		8/02/2013	131						
788dN3bCvCw			4	15/10/2012	GP		8/02/2013	116						
788dN3bCvCw			4	15/10/2012	GP		1/12/2013	412						
788dN3bCvCw			4	15/10/2012	GP		1/12/2013	412						
788dN3bCvCw			4	15/10/2012	GP		15/11/2013	396	O049 from NMDS and rx matching dates					
788dN3bCvCw			4	22/04/2015	GP		28/08/2015	128					TOP	
788dN3bCvCw			4	7/05/2015	GP		28/08/2015	113					TOP	
788dN3bCvCw			4	3/06/2015	GP		28/08/2015	86					TOP	7 rx then TOP 3.5 months later; then a second TOP 9 months later (no more iso during interim) with complications two weeks late

In the example above, the 'dispense date' column shows isotretinoin was dispensed 7 times between 24 November 2011 and 15 October 2012. A GP wrote six prescriptions and a dermatologist provided one.

Over this one-year period this patient had one TOP on 8 February 2013, another TOP on 15 November 2013, and a spontaneous abortion on 1 December 2013. The first TOP was 116 days after a prescription for isotretinoin and so it was counted as being during the period that was potentially linked to isotretinoin.

The second TOP was > 396 days after her most recent prescription for isotretinoin so it was not counted as being likely related to isotretinoin. There are no dates in the 'Decision Support dates' column so decision support was not used for this patient.

2. Potentially exposed live birth

Example 2: Data illustrating identification of a potentially exposed live birth

eNHI	ETHNIC	dhb	DE	dispense date	speciality	DS Date	date_event_ended	days between date dispensed and ho	diag1002	diag1003	diag1004	diag1005	ClinicalCodeDescription	Comments and story
7cHMZwRvN6g			2	21/06/2012	Dermatology		21/08/2013	426						
7cHMZwRvN6g			2	26/07/2012	Dermatology		21/08/2013	391						
7cHMZwRvN6g			2	10/09/2012	Dermatology		21/08/2013	345						
7cHMZwRvN6g			2	5/11/2012	Dermatology		21/08/2013	289						NB: two potential isotretinoin related maternity events
7cHMZwRvN6g			2	21/01/2013	Dermatology		21/08/2013	212						
7cHMZwRvN6g			2	8/05/2013	Dermatology		21/08/2013	105						
7cHMZwRvN6g			2	25/07/2013	Dermatology		21/08/2013	27	O049 from NMDS and rx matching dates					
7cHMZwRvN6g			2	19/11/2013	Dermatology									
7cHMZwRvN6g			2	7/03/2014	GP		3/03/2015	361					Single live birth 7 rx then TOP 4 weeks later then resumed iso and on 7Mar14 had 84 days supply stat then live birth 12 months later	

In this example isotretinoin was dispensed on 21 June, 26 July, 10 September, and 5 November of 2012 and on 21 January 2013. After a break there were then two more dispensings on 8 May and 25 July 2013.

The July dispensing was followed four weeks later by a TOP on 21 Aug 2013, after which she was dispensed her final dermatologist prescription in the study period on 19 Nov 2013 and then a GP-prescribed dispensing on 7 March 2014. This dispensing was almost exactly 12 months before a live birth on 3 March 2015 so would have been within the guidelines if it was for 30 days' supply. However the usage data showed this GP dispensing was for 84 days' supply, so if this woman took all dispensed doses, waited four weeks before becoming pregnant, and had a full term pregnancy, a baby born before 7 April 2015 would potentially be exposed to isotretinoin. Her baby born on 3 March 2015 could potentially have been exposed at the critical time of 2-5 weeks post conception.[49]

Having completed the 'stories' of patients who had maternity events within 15 months of an isotretinoin prescription I counted the number of events. I identified all the NHI codes for women who had a TOP within eight months of an isotretinoin prescription and all live births within 400 days of an isotretinoin prescription during the study period. This conclusion has been supported by subsequent further checks completed between the various datasets.

3. *Example of Decision Support use and TOP*

Example 3: Data illustrating identification of Decision Support use and TOP

eNHI	ETHN	dhb	D	dispense date	specialit	DS Date	date_event_ ended	days between date	Comments and story
tuYxp.VgyBI			3	22/02/2011	Dermatology				
tuYxp.VgyBI			3	28/03/2011	Dermatology				
tuYxp.VgyBI			3	3/08/2013	GP		21/02/2014	202	
tuYxp.VgyBI			3	8/10/2013	GP		21/02/2014	136	
tuYxp.VgyBI			3	27/11/2013	GP	12/11/2013	21/02/2014	86	
tuYxp.VgyBI			3	8/01/2014	GP	12/11/2013	21/02/2014	44	
tuYxp.VgyBI			3	14/02/2014	GP	12/11/2013	21/02/2014	7	2 rx derm then break then 5 rx GP then TOP 7 days later - DS used before last 3 month Rx

EncryptedHCUID	DateDispensed	ChemicalName	FormulationNam	NumberOfItems	providertype	RepeatSequence	Dose	DaysSupply	Sex	PatientAge	EthnicCode
tuYxp.VgyBI	2013-08-03	Isotretinoin	Cap 20 mg	1	M	1	1	30	F		
tuYxp.VgyBI	2013-10-08	Isotretinoin	Cap 20 mg	1	M	2	1	30	F		
tuYxp.VgyBI	2013-11-27	Isotretinoin	Cap 20 mg	1	M	1	1	30	F		
tuYxp.VgyBI	2014-01-08	Isotretinoin	Cap 20 mg	1	M	2	1	30	F		
tuYxp.VgyBI	2014-02-14	Isotretinoin	Cap 20 mg	1	M	3	1	30	F		

In the example illustrated above isotretinoin was prescribed by a dermatologist in 2011 and by a GP in August and October 2013. Decision support was used on 12 November 2013 and a prescription presented on 27 November 2013. Repeat dispensings were collected 8 January 2014 and 14 February 2014 and the patient had a TOP on 21 February 2014. In this example isotretinoin was dispensed more than 90 days after decision support was used and a TOP occurred a week after the final dispensing.

4. *Example of Decision Support use and exposed live birth*

Example 4: Data illustrating identification of Decision Support use and a potentially exposed live birth

eNHI	ETHN	dhb	DE	dispense dat	speciality	DS Date	date_event	Days % disp & ev	Days % DS & d	ICD10v	All_diag1004
IY8U7tU1Y9Y			5	26/04/2014	GP	23/01/2014	1/03/2015	309	-92	Z370	
IY8U7tU1Y9Y			5	18/03/2014	GP	23/01/2014	1/03/2015	348	-53	Z370	5 rx (last 30 days) then live birth 9 months later
IY8U7tU1Y9Y			5	13/12/2013	GP		1/03/2015	443		Z370	
IY8U7tU1Y9Y			5	15/01/2014	GP		1/03/2015	410		Z370	
IY8U7tU1Y9Y			5	30/05/2014	GP		1/03/2015	275		Z370	

In this example isotretinoin was dispensed on 13 December 2013 and 15 January 2014 for 30 days' supply each time with no repeats. Decision support was used 23 January 2014 but the first dispensing of this new prescription did not occur for 53 days (nearly eight weeks) until 18 March 2014. As the prescription included two repeats which were collected 26 April 2014 and 30 May 2014, it was over four months (126 days) after decision support was used that the final dispensing of this prescription was made. The woman then went on and had a live birth on 1 March 2015 which was 275 days later – well before the guideline recommendation of 11 months (340 days).

Appendix C: Ethics Approval Letter HD15/027

HD15/027

Academic Services
Manager, Academic Committees, Mr Gary Witte

28 August 2015

Professor S Dovey
Department of General Practice & Rural Health
Dunedin School of Medicine
University of Otago Medical School

Dear Professor Dovey,

I am writing to you concerning your proposal entitled "**Health outcomes and access following regulatory changes for Isotretinoin prescribing in New Zealand**", Ethics Committee reference number **HD15/027**.

The above research was submitted and reviewed as ' Human Ethics Committee (Health) Departmental Conditional Approval of Projects using Health Information'. The outcome of that consideration was that the proposal was **approved.**

The standard conditions of approval for all human research projects reviewed and approved by the Committee are the following:

Conduct the research project strictly in accordance with the research proposal submitted and granted ethics approval, including any amendments required to be made to the proposal by the Human Research Ethics Committee.

Inform the Human Research Ethics Committee immediately of anything which may warrant review of ethics approval of the research project, including: serious or unexpected adverse effects on participants; unforeseen events that might affect continued ethical acceptability of the project; and a written report about these matters must be submitted to the Academic Committees Office by no later than the next working day after recognition of an adverse occurrence/event. Please note that in cases of adverse events an incident report should also be made to the Health and Safety Office:

http://www.otago.ac.nz/healthandsafety/index.html

Advise the Committee in writing as soon as practicable if the research project is discontinued.

Make no change to the project as approved in its entirety by the Committee, including any wording in any document approved as part of the project, without prior written approval of the Committee for any change. If you are applying for an amendment to your approved research, please email your request to the Academic Committees Office:

gary.witte@otago.ac.nz

jo.farrondediaz@otago.ac.nz

Approval is for up to three years from the date of this letter. If this project has not been completed within three years from the date of this letter, re-approval or an extension of approval must be requested. If the nature, consent, location, procedures or personnel of your approved application change, please advise me in writing.

Approval is for up to three years from the date of this letter. If this project has not been completed within three years from the date of this letter, re-approval must be requested. If the nature, consent, location, procedures or personnel of your approved application change, please advise me in writing.

Yours sincerely,

Mr Gary Witte
Manager, Academic Committees
Tel: 479 8256
Email: gary.witte@otago.ac.nz

c.c. Assoc. Prof. C Jaye Head of Department Department of General Practice & Rural Health

Appendix D: Maori Consultation Letter 15 September 2015

NGĀI TAHU RESEARCH CONSULTATION COMMITTEE
TE KOMITI RAKAHAU KI KAI TAHU

Tuesday, 15 September 2015.

Dr Alesha Smith,
School of Pharmacy,
DUNEDIN.

Tēnā Koe Dr Alesha Smith,

Health Outcomes and Access following Regulatory Changes for Isotretinoin Prescribing in New Zealand

The Ngāi Tahu Research Consultation Committee (the committee) met on Tuesday, 15 September 2015 to discuss your research proposition.

By way of introduction, this response from The Committee is provided as part of the Memorandum of Understanding between Te Rūnanga o Ngāi Tahu and the University. In the statement of principles of the memorandum it states "Ngāi Tahu acknowledges that the consultation process outline in this policy provides no power of veto by Ngāi Tahu to research undertaken at the University of Otago". As such, this response is not "approval" or "mandate" for the research, rather it is a mandated response from a Ngāi Tahu appointed committee. This process is part of a number of requirements for researchers to undertake and does not cover other issues relating to ethics, including methodology they are separate requirements with other committees, for example the Human Ethics Committee, etc.

Within the context of the Policy for Research Consultation with Māori, the Committee base consultation on that defined by Justice McGechan:

"Consultation does not mean negotiation or agreement. It means: setting out a proposal not fully decided upon; adequately informing a party about relevant information upon which the proposal is based; listening to what the others have to say with an open mind (in that there is room to be persuaded against the proposal); undertaking that task in a genuine and not cosmetic manner. Reaching a decision that may or may not alter the original proposal."

The Committee considers the research to be of importance to Māori health.

The Committee commends the researchers for recording ethnicity where available.

The Committee suggests dissemination of the research findings to Māori health organisations regarding this study.

We wish you every success in your research and the committee also requests a copy of the research findings.

The Ngāi Tahu Research Consultation Committee has membership from:
Te Rūnanga o Ōtākou Incorporated
Kāti Huirapa Rūnaka ki Puketeraki
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NGĀI TAHU RESEARCH CONSULTATION COMMITTEE
TE KOMITI RAKAHAU KI KAI TAHU

This letter of suggestion, recommendation and advice is current for an 18 month period from Tuesday, 15 September 2015 to 15 March 2017.

Nāhaku noa, nā

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